(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
16 November 2017 (16.11.2017)

WIPO | PCT

(10) International Publication Number
WO 2017/197045 A1

(51) International Patent Classification:
C07D 209/56 (2006.01) *C07D 223/14* (2006.01)
C07D 221/02 (2006.01)

(21) International Application Number:
PCT/US2017/032040

(22) International Filing Date:
10 May 2017 (10.05.2017)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
62/334,826 11 May 2016 (11.05.2016) US

(72) Inventors; and

(71) Applicants: **MOVASSAGHI, Mohammad** [US/US]; 49 Fisher Road, Arlington, Massachusetts 02476 (US). **LATHROP, Stephen Paul** [US/US]; 1712 York Avenue, San Mateo, California 94401 (US). **POMPEO, Matthew M.** [CA/US]; 235 Albany Street, Apt. 4099, Cambridge, Massachusetts 02139 (US). **CHANG, Wen-Tau Timothy** [US/US]; 72 Pinehurst Avenue, Billerica, Massachusetts 01821 (US).

(74) Agent: **BLINKA, Thomas A.** et al.; Cooley LLP, 1299 Pennsylvania Avenue, NW, Suite 700, Washington, District of Columbia 20004 (US).

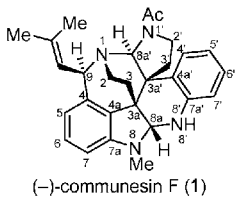
(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BN, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DJ, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IR, IS, JP, KE, KG, KH, KN, KP, KR, KW, KZ, LA, LC, LK, LR, LS, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PA, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SA, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, ST, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, RU, TJ, TM), European (AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, KM, ML, MR, NE, SN, TD, TG).

Published:
— *with international search report (Art. 21(3))*

(54) Title: CONVERGENT AND ENANTIOSELECTIVE TOTAL SYNTHESIS OF COMMUNESIN ANALOGS

FIG. 4



(–)-communesin F (1)

(57) Abstract: A highly convergent biomimetic synthesis of a complex polycyclic scaffold has been successfully implemented. From these efforts, compounds having a structure of Formula (I) or a pharmaceutically acceptable salt, tautomer or stereoisomer thereof, wherein R^1-R^8 and m, n, r, s, t, and u are as defined herein, is provided. Methods of making such compounds are also disclosed as are methods for the treatment of cancer, various infectious diseases, and abnormal cardiovascular function.

WO 2017/197045 A1

CONVERGENT AND ENANTIOSELECTIVE TOTAL SYNTHESIS OF COMMUNESIN ANALOGS

CROSS-REFERENCE TO RELATED APPLICATION

[0001] This application claims the benefit of and priority to U.S. Provisional Application No. 62/334,826, filed on May 11, 2016 and entitled "CONVERGENT AND BIOMIMETIC ENANTIOSELECTIVE TOTAL SYNTHESIS OF (–)-COMMUNESIN F," the disclosure of which is hereby incorporated by reference in its entirety for all purposes.

STATEMENT OF GOVERNMENT INTEREST

[0002] This invention was made with Government support under Grant No. R01 GM089732 awarded by the National Institutes of Health, and under Grant No. CHE-1212527 awarded by the National Science Foundation. The United States Government has certain rights in the invention.

BACKGROUND

[0003] The communesin alkaloids are a family of nine structurally complex natural products isolated from various marine and terrestrial *Penicillium* fungi (FIG. 1). Some members have been shown to possess insecticidal and antiproliferative activities as well as significant cytotoxicity against lymphocytic leukemia. Communesins A (**2**) and B (**4**), first isolated in 1993 by Numata were found to exhibit moderate to potent cytotoxicity against cultured mouse P-388 lymphocytic leukemia cells (ED_{50} = 3.5 μg/mL and 0.45 μg/mL, respectively). (Numata, A.; Takahashi, C.; Ito, Y.; Takada, T.; Kawai, K.; Usami, Y.; Imachi, M.; Ito, T.; Hasegawa, T. *Tetrahedron Lett.* **1993**, *34*, 2355–2358.) In 2004, Jadulco and co-workers isolated communesins C (**5**) and D (**6**) and, together with **4**, were shown to possess moderate anti-proliferative activity against an array of human leukemia cell lines (Table 1). Furthermore, compounds **4**, **5** and **6** exhibited toxicity against the brine shrimp *Artemia salina* with LD_{50} values of 0.30, 1.96, and 0.57 μg/mL, respectively. (Jadulco, R.; Edrada, R. A.; Ebel, R.; Berg, A.; Schaumann, K.; Wray, V.; Steube, K.; Proksch, P. *J. Nat. Prod.* **2004**, *67*, 78–81.)

[0004] Later in 2004, Hayashi and co-workers isolated communesins E (**3**) and F (**1**) and studied the insecticidal properties of these new derivatives together with **2**, **4**, and **6**. (Hayashi, H.; Matsumoto, H.; Akiyama, K. *Biosci. Biotechnol. Biochem.* **2004**, *68*, 753–756.) Communesin B (**4**) was found to be the most active against third instar larvae of silkworms with an LD_{50} value of 5 μg/g of diet by oral administration. Communesins A (**2**), D (**6**), E (**3**), and F (**1**) were found to exhibit lower insecticidal activities.

[0005] Recently, in 2015, Fan and co-workers isolated communesin I (**9**) and studied the cardiovascular effects of this new alkaloid, together with co-isolates **2** and **4**. (Fan, Y.-Q.; Li, P.-H.; Chao, Y.-X.; Chen, H.; Du, N.; He, Q.-X.; Liu, K.-C. *Mar. Drugs.* **2015**, *13*, 6489–6504.) All three compounds showed a significant mitigative effect on bradycardia caused by astemidazole at different concentrations. In addition, communesins I (**9**) and A (**2**) exhibited moderate vasculogenetic activity. Finally, compounds **9** and **2** were found to moderately promote the function of cardiovascular vessels.

[0006] The core structures of the communesins share a unique heptacyclic skeleton containing two aminals and at least five stereogenic centers, of which two are vicinal and quaternary (FIG. 1). To date, the total synthesis of (±)-communesin F (**1**) has been completed by Qin, Weinreb, and Funk, in addition to a formal synthesis by Stoltz. Ma's total synthesis of (–)-communesin F (**1**) remains the only enantioselective solution for this archetypical alkaloid. However, these total syntheses are complex, low yielding, and do not readily lend themselves to the synthesis of analogs or derivatives of (–)-**1**, which would be necessary to support a rational drug development program.

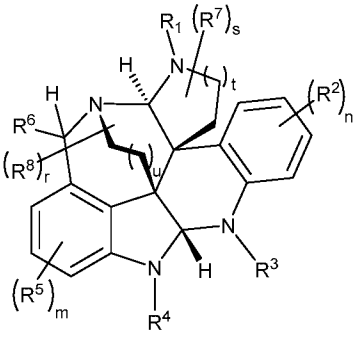
[0007] The exquisite structural complexity, coupled with an array of interesting biological properties has prompted the present disclosure of a novel, efficient, and convergent chemical synthesis of the communesin alkaloids. These methods involve the stereocontrolled oxidative union of two dissimilar tryptamine derivatives followed by reorganization of a C3a–C3a' linked heterodimer to develop a highly convergent total synthesis that would be suitable for the preparation of diverse analogs derived from the family of communesins.

[0008] Herein, are presented concise enantioselective total syntheses of several representative communesins, ready for adaption toward a wide range of previously unexplored analogs. The highly convergent route establishes inventive methods that allow for unprecedented efficiency in constructing the complex heptacyclic ring system from two densely functionalized building blocks. In addition, the use of flexible stereochemical control elements enables access to any selected enantiomer or diastereomer without dramatic alterations to the strategy, and is easily generalized and applied to the synthesis of a wide variety of analogs. This novel chemical synthesis allows, for the first time, the opportunity to fully explore the promising biological properties of this class of compounds.

BRIEF SUMMARY

[0009] Various inventive embodiments are disclosed that are generally directed to a highly convergent biomimetic enantioselective synthesis of alkaloid compounds of Formula (I), as well as compounds and methods of use of Formula (I), as described herein.

[0010] In one embodiment, the present disclosure relates to compounds of Formula (I):



Formula (I)

or a pharmaceutically acceptable salt, tautomer or stereoisomer thereof is described, wherein:

R^1, R^3, and R^4 are each independently selected from H, C_1-C_{12} alkyl, C_2-C_{12} alkenyl, C_2-C_{12} alkynyl, -C(=O)R^9, -C(=O)NR^9R^{10}, -S(=O)$_u$$R^{12}$, aryl, heteroaryl, carbocyclyl, or heterocyclyl, wherein R^3 and R^4 taken together with the carbon atoms to which they are attached form an aryl, heteroaryl, carbocyclic, or heterocyclic ring;

R^2 and R^5 are each independently selected from F, Cl, Br, I, -OH, -OR^9, -OC(=O)R^9, -S(=O)$_u$$R^{12}$, -$NR^9R^{10}$, C_1-C_{12} alkyl, C_2-C_{12} alkenyl, C_2-C_{12} alkynyl, aryl, heteroaryl, carbocyclyl, or heterocyclyl;

R^6 is independently H, -OH, -OR^9, -OC(=O)R^9, -S(=O)$_u$$R^{12}$, -$NR^9R^{10}$, C_1-C_{12} alkyl, C_1-C_{12} alkyl, C_2-C_{12} alkenyl, C_2-C_{12} alkynyl aryl, heteroaryl, carbocyclyl, or heterocyclyl;

R^7 and R^8 are each independently selected from H, C_1-C_{12} alkyl; C_2-C_{12} alkenyl, C_2-C_{12} alkynyl, -C(=O)R^9, -C(=O)NR^9R^{10}, -S(=O)$_u$$R^{12}$, -OH, -$OR^9$, -OC(=O)$R^9$, -$NR^9R^{10}$, aryl, heteroaryl, carbocyclyl, or heterocyclyl, wherein two R^7 or two R^8 groups taken together with the carbon atoms to which they are attached form an aryl, heteroaryl, carbocyclic, or heterocyclic ring;

R^9 and R^{10} are each independently selected from H, C_1-C_{12} alkyl, C_2-C_{12} alkenyl, C_2-C_{12} alkynyl, aryl, heteroaryl, carbocyclyl, or heterocyclyl, wherein R^9 and R^{10} taken together with the carbon atoms to which they are attached form an aryl, heteroaryl, carbocyclic, or heterocyclic ring;

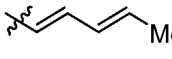
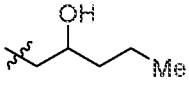
R^{12} is C_1-C_{12} alkyl, C_2-C_{12} alkenyl, C_2-C_{12} alkynyl, aryl, heteroaryl, carbocyclyl, heterocyclyl, -$(CH_2)_n$$SiMe_3$, or -$(CH_2)_n$$R^9$;

m and t are each independently an integer from 0 to 3;

n, r, s, and v are each independently an integer from 0 to 4; and

u is 0, 1, or 2;

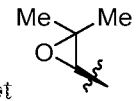
with the following provisos:

when R^1 is  , wherein R^{11} is Me, Et, *n*-Pr,  , or  ;

R^4 is Me;

m, n, r, and s are 0;

t and u are 1; then

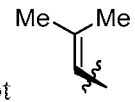
R^6 is not  ; and

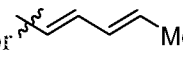
when R^1 is  , wherein R^{11} is Me;

R^4 is Me;

m, n, r, and s are 0;

t and u are 1; then

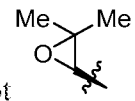
R^6 is not  ; and

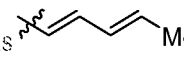
when R^1 is  , wherein R^{11} is Me, or  ;

R^4 is H;

m, n, r, and s are 0;

t and u are 1; then

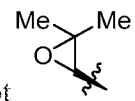
R^6 is not  ; and

when R^1 is  , wherein R^{11} is  ;

R^4 is -CHO;

m, n, r, and s are 0;

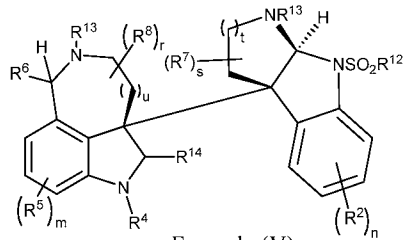
t and u are 1; and

R^6 is not  .

[0011] In one embodiment, the present disclosure relates to a pharmaceutical composition comprising a compound of Formula (I) and a pharmaceutically acceptable excipient.

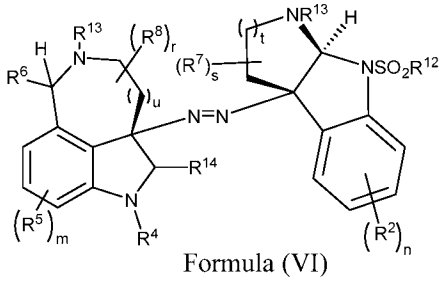
[0012] In another embodiment, the present disclosure provides a method of treating a disease or condition comprising administering an effective amount of the pharmaceutical composition to a subject. In some embodiments, the disease or condition is cancer. In other embodiments, the disease or condition is a bacterial infection. In other embodiments, the disease or condition is a fungal infection. In another embodiment, the disease or condition is a viral infection. In still other embodiments, the disease or condition is abnormal cardiovascular function. In yet another embodiment, the pharmaceutical compositions are used to treat insect infestations.

[0013] In one embodiment, the disclosure provides a method of making compounds of Formula (I) by a rearrangement of:



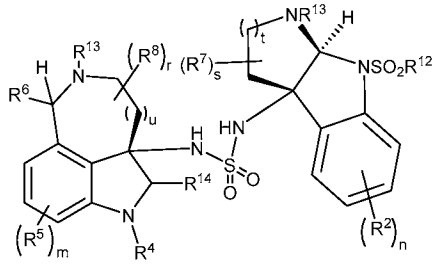
Formula (V)

[0014] In another embodiment, the present disclosure provides a method of making compounds of Formula (V) by a radical recombination reaction of, e.g., by photochemical degradation of the azo group:



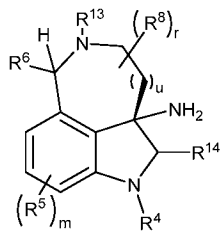
Formula (VI)

[0015] In another embodiment, the present disclosure provides a method of making compounds of Formula (VI) by the extrusion of sulfur dioxide from:

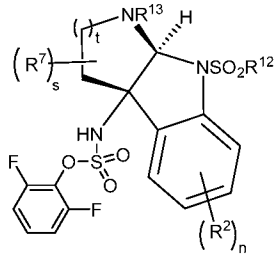


Formula (VII)

[0016] In still another embodiment, the present disclosure provides a method of making compounds of Formula (VII) by a reaction (e.g., nucleophilic substitution reaction) between compounds of Formula (III) and Formula (VIII):

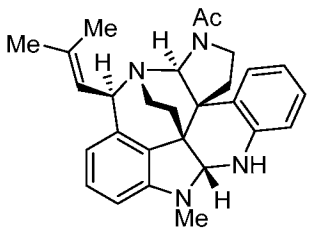


Formula (III)



Formula (VIII)

[0017] In one embodiment, the first biomimetic enantioselective total synthesis of (-)-communesin F based on a late-stage heterodimerization and aminal exchange is described. It is to be understood that these methods and approaches can be generalized and applied to the synthesis of a variety of compounds, including various communesin derivatives, such as those represented by Formula (I).



(–)-communesin F

BRIEF DESCRIPTION OF THE FIGURES

[0018] The skilled artisan will understand that the drawings primarily are for illustrative purposes and are not intended to limit the scope of the inventive subject matter described herein.

[0019] **FIG. 1** shows the chemical structures of the naturally occurring communesin alkaloids.

[0020] **FIG. 2** is a ^{1}H NMR spectrum for (–)-communesin F prepared by the methods described herein.

[0021] **FIG. 3** is a ^{13}C NMR spectrum for (–)-communesin F prepared by the methods described herein.

[0022] **FIG. 4** shows the positional numbering system used for the (–)-communesin F core.

DETAILED DESCRIPTION

[0023] In the following description, certain specific details are set forth in order to provide a thorough understanding of various embodiments. However, one skilled in the art will understand that the invention can be practiced without these details. In other instances, well-known structures have not been shown or described in detail to avoid unnecessarily obscuring descriptions of the embodiments.

[0024] All definitions, as defined and used herein, should be understood to control over dictionary definitions, definitions in documents incorporated by reference, and/or ordinary meanings of the defined terms. Use of flow diagrams is not meant to be limiting with respect to the order of operations performed for all embodiments. The indefinite articles "a" and "an," as used herein in the specification and in the claims, unless clearly indicated to the contrary, should be understood to mean "at least one."

[0025] Reference throughout this specification to "one embodiment" or "an embodiment," etc. means that a particular feature, structure or characteristic described in connection with the embodiment is included in at least one embodiment. Thus, the appearances of the phrases "in one embodiment" or "in an embodiment" in various places throughout this specification are not necessarily all referring to the same embodiment. Furthermore, the particular features, structures, or characteristics can be combined in any suitable manner in one or more embodiments. Also, as used in this specification and the appended claims, the singular forms "a," "an," and "the" include plural referents unless the content clearly dictates otherwise. It should also be noted that the term "or" is generally employed in its sense including "and/or" unless the content clearly dictates otherwise.

[0026] As used herein in the specification and in the claims, the phrase "at least one," in reference to a list of one or more elements, should be understood to mean at least one element selected from any one or more of the elements in the list of elements, but not necessarily including at least one of each and every element specifically listed within the list of elements and not excluding any combinations of elements in the list of elements. This definition also allows

that elements may optionally be present other than the elements specifically identified within the list of elements to which the phrase "at least one" refers, whether related or unrelated to those elements specifically identified. Thus, as a non-limiting example, "at least one of A and B" (or, equivalently, "at least one of A or B," or, equivalently "at least one of A and/or B") can refer, in one embodiment, to at least one, optionally including more than one, A, with no B present (and optionally including elements other than B); in another embodiment, to at least one, optionally including more than one, B, with no A present (and optionally including elements other than A); in yet another embodiment, to at least one, optionally including more than one, A, and at least one, optionally including more than one, B (and optionally including other elements); etc.

[0027] In the claims, as well as in the specification above, all transitional phrases such as "comprising," "including," "carrying," "having," "containing," "involving," "holding," "composed of," and the like are to be understood to be open-ended, i.e., to mean including but not limited to. Only the transitional phrases "consisting of" and "consisting essentially of" shall be closed or semi-closed transitional phrases, respectively, as set forth in the United States Patent Office Manual of Patent Examining Procedures, Section 2111.03.

[0028] "Alkyl" or "alkyl group" refers to a fully saturated, straight or branched hydrocarbon chain radical, and which is attached to the rest of the molecule by a single bond. Alkyls comprising any number of carbon atoms from 1 to 12 are included. An alkyl comprising up to 12 carbon atoms is a C_1-C_{12} alkyl, an alkyl comprising up to 10 carbon atoms is a C_1-C_{10} alkyl, an alkyl comprising up to 6 carbon atoms is a C_1-C_6 alkyl and an alkyl comprising up to 5 carbon atoms is a C_1-C_5 alkyl. A C_1-C_5 alkyl includes C_5 alkyls, C_4 alkyls, C_3 alkyls, C_2 alkyls and C_1 alkyl (*i.e.*, methyl). A C_1-C_6 alkyl includes all moieties described above for C_1-C_5 alkyls but also includes C_6 alkyls. A C_1-C_{10} alkyl includes all moieties described above for C_1-C_5 alkyls and C_1-C_6 alkyls, but also includes C_7, C_8, C_9 and C_{10} alkyls. Similarly, a C_1-C_{12} alkyl includes all the foregoing moieties, but also includes C_{11} and C_{12} alkyls. Non-limiting examples of C_1-C_{12} alkyl include methyl, ethyl, *n*-propyl, *i*-propyl, *sec*-propyl, *n*-butyl, *i*-butyl, *sec*-butyl, *t*-butyl, *n*-pentyl, *t*-amyl, *n*-hexyl, *n*-heptyl, *n*-octyl, *n*-nonyl, *n*-decyl, *n*-undecyl, and *n*-dodecyl. Unless stated otherwise specifically in the specification, an alkyl group can be optionally substituted.

[0029] "Alkylene" or "alkylene chain" refers to a fully saturated, straight or branched divalent hydrocarbon chain radical. Alkylenes comprising any number of carbon atoms from 1 to 12 are included. Non-limiting examples of C_1-C_{12} alkylene include methylene, ethylene, propylene, *n*-butylene, ethenylene, propenylene, *n*-butenylene, propynylene, *n*-butynylene, and the like. The alkylene chain is attached to the rest of the molecule through a single bond and to

the radical group through a single bond. The points of attachment of the alkylene chain to the rest of the molecule and to the radical group can be through one carbon or any two carbons within the chain. Unless stated otherwise specifically in the specification, an alkylene chain can be optionally substituted.

[0030] "Alkenyl" or "alkenyl group" refers to a straight or branched hydrocarbon chain radical having from two to twelve carbon atoms, and having one or more carbon-carbon double bonds. Each alkenyl group is attached to the rest of the molecule by a single bond. Alkenyl group comprising any number of carbon atoms from 2 to 12 are included. An alkenyl group comprising up to 12 carbon atoms is a C_2-C_{12} alkenyl, an alkenyl comprising up to 10 carbon atoms is a C_2-C_{10} alkenyl, an alkenyl group comprising up to 6 carbon atoms is a C_2-C_6 alkenyl and an alkenyl comprising up to 5 carbon atoms is a C_2-C_5 alkenyl. A C_2-C_5 alkenyl includes C_5 alkenyls, C_4 alkenyls, C_3 alkenyls, and C_2 alkenyls. A C_2-C_6 alkenyl includes all moieties described above for C_2-C_5 alkenyls but also includes C_6 alkenyls. A C_2-C_{10} alkenyl includes all moieties described above for C_2-C_5 alkenyls and C_2-C_6 alkenyls, but also includes C_7, C_8, C_9 and C_{10} alkenyls. Similarly, a C_2-C_{12} alkenyl includes all the foregoing moieties, but also includes C_{11} and C_{12} alkenyls. Non-limiting examples of C_2-C_{12} alkenyl include ethenyl (vinyl), 1-propenyl, 2-propenyl (allyl), iso-propenyl, 2-methyl-1-propenyl, 1-butenyl, 2-butenyl, 3-butenyl, 1-pentenyl, 2-pentenyl, 3-pentenyl, 4-pentenyl, 1-hexenyl, 2-hexenyl, 3-hexenyl, 4-hexenyl, 5-hexenyl, 1-heptenyl, 2-heptenyl, 3-heptenyl, 4-heptenyl, 5-heptenyl, 6-heptenyl, 1-octenyl, 2-octenyl, 3-octenyl, 4-octenyl, 5-octenyl, 6-octenyl, 7-octenyl, 1-nonenyl, 2-nonenyl, 3-nonenyl, 4-nonenyl, 5-nonenyl, 6-nonenyl, 7-nonenyl, 8-nonenyl, 1-decenyl, 2-decenyl, 3-decenyl, 4-decenyl, 5-decenyl, 6-decenyl, 7-decenyl, 8-decenyl, 9-decenyl, 1-undecenyl, 2-undecenyl, 3-undecenyl, 4-undecenyl, 5-undecenyl, 6-undecenyl, 7-undecenyl, 8-undecenyl, 9-undecenyl, 10-undecenyl, 1-dodecenyl, 2-dodecenyl, 3-dodecenyl, 4-dodecenyl, 5-dodecenyl, 6-dodecenyl, 7-dodecenyl, 8-dodecenyl, 9-dodecenyl, 10-dodecenyl, and 11-dodecenyl. Examples of C_1-C_3 alkyl includes methyl, ethyl, *n*-propyl, and *i*-propyl. Examples of C_1-C_4 alkyl includes methyl, ethyl, *n*-propyl, *i*-propyl, *n*-butyl, *i*-butyl, and *sec*-butyl. Unless stated otherwise specifically in the specification, an alkyl group can be optionally substituted.

[0031] "Alkenylene" or "alkenylene chain" refers to a straight or branched divalent hydrocarbon chain radical, having from two to twelve carbon atoms, and having one or more carbon-carbon double bonds. Non-limiting examples of C_2-C_{12} alkenylene include ethene, propene, butene, and the like. The alkenylene chain is attached to the rest of the molecule through a single bond and to the radical group through a single bond. The points of attachment of

the alkenylene chain to the rest of the molecule and to the radical group can be through one carbon or any two carbons within the chain. Unless stated otherwise specifically in the specification, an alkenylene chain can be optionally substituted.

[0032] "Alkynyl" or "alkynyl group" refers to a straight or branched hydrocarbon chain radical having from two to twelve carbon atoms, and having one or more carbon-carbon triple bonds. Each alkynyl group is attached to the rest of the molecule by a single bond. Alkynyl groups comprising any number of carbon atoms from 2 to 12 are included. An alkynyl group comprising up to 12 carbon atoms is a C_2-C_{12} alkynyl, an alkynyl comprising up to 10 carbon atoms is a C_2-C_{10} alkynyl, an alkynyl group comprising up to 6 carbon atoms is a C_2-C_6 alkynyl and an alkynyl comprising up to 5 carbon atoms is a C_2-C_5 alkynyl. A C_2-C_5 alkynyl includes C_5 alkynyls, C_4 alkynyls, C_3 alkynyls, and C_2 alkynyls. A C_2-C_6 alkynyl includes all moieties described above for C_2-C_5 alkynyls but also includes C_6 alkynyls. A C_2-C_{10} alkynyl includes all moieties described above for C_2-C_5 alkynyls and C_2-C_6 alkynyls, but also includes C_7, C_8, C_9 and C_{10} alkynyls. Similarly, a C_2-C_{12} alkynyl includes all the foregoing moieties, but also includes C_{11} and C_{12} alkynyls. Non-limiting examples of C_2-C_{12} alkenyl include ethynyl, propynyl, butynyl, pentynyl and the like. Unless stated otherwise specifically in the specification, an alkyl group can be optionally substituted.

[0033] "Alkynylene" or "alkynylene chain" refers to a straight or branched divalent hydrocarbon chain radical, having from two to twelve carbon atoms, and having one or more carbon-carbon triple bonds. Non-limiting examples of C_2-C_{12} alkynylene include ethynylene, propargylene and the like. The alkynylene chain is attached to the rest of the molecule through a single bond and to the radical group through a single bond. The points of attachment of the alkynylene chain to the rest of the molecule and to the radical group can be through one carbon or any two carbons within the chain. Unless stated otherwise specifically in the specification, an alkynylene chain can be optionally substituted.

[0034] "Alkoxy" refers to a radical of the formula $-OR_a$ where R_a is an alkyl, alkenyl or alknyl radical as defined above containing one to twelve carbon atoms. Unless stated otherwise specifically in the specification, an alkoxy group can be optionally substituted.

[0035] "Alkylamino" refers to a radical of the formula $-NHR_a$ or $-NR_aR_a$ where each R_a is, independently, an alkyl, alkenyl or alkynyl radical as defined above containing one to twelve carbon atoms. Unless stated otherwise specifically in the specification, an alkylamino group can be optionally substituted.

[0036] "Alkylcarbonyl" refers to the –C(=O)R_a moiety, wherein R_a is an alkyl, alkenyl or alkynyl radical as defined above. A non-limiting example of an alkyl carbonyl is the methyl carbonyl ("acetal") moiety. Alkylcarbonyl groups can also be referred to as "Cw-Cz acyl" where w and z depicts the range of the number of carbon in R_a, as defined above. For example, "C1-C_{10} acyl" refers to alkylcarbonyl group as defined above, where R_a is C_1-C_{10} alkyl, C_1-C_{10} alkenyl, or C_1-C_{10} alkynyl radical as defined above. Unless stated otherwise specifically in the specification, an alkyl carbonyl group can be optionally substituted.

[0037] "Aryl" refers to a hydrocarbon ring system radical comprising hydrogen, 6 to 18 carbon atoms and at least one aromatic ring. For purposes of this invention, the aryl radical can be a monocyclic, bicyclic, tricyclic or tetracyclic ring system, which can include fused or bridged ring systems. Aryl radicals include, but are not limited to, aryl radicals derived from aceanthrylene, acenaphthylene, acephenanthrylene, anthracene, azulene, benzene, chrysene, fluoranthene, fluorene, *as*-indacene, *s*-indacene, indane, indene, naphthalene, phenalene, phenanthrene, pleiadene, pyrene, and triphenylene. Unless stated otherwise specifically in the specification, the term "aryl" is meant to include aryl radicals that are optionally substituted.

[0038] "Aralkyl" refers to a radical of the formula -R_b-R_c where R_b is an alkylene, alkenylene or alkynylene group as defined above and R_c is one or more aryl radicals as defined above, for example, benzyl, diphenylmethyl and the like. Unless stated otherwise specifically in the specification, an aralkyl group can be optionally substituted.

[0039] "Carbocyclyl," "carbocyclic ring" or "carbocycle" refers to a rings structure, wherein the atoms which form the ring are each carbon. Carbocyclic rings can comprise from 3 to 20 carbon atoms in the ring. Carbocyclic rings include aryls and cycloalkyl, cycloalkenyl and cycloalkynyl as defined herein. Unless stated otherwise specifically in the specification, a carbocyclyl group can be optionally substituted.

[0040] "Cycloalkyl" refers to a stable non-aromatic monocyclic or polycyclic fully saturated hydrocarbon radical consisting solely of carbon and hydrogen atoms, which can include fused or bridged ring systems, having from three to twenty carbon atoms, preferably having from three to ten carbon atoms, and which is attached to the rest of the molecule by a single bond. Monocyclic cycloalkyl radicals include, for example, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, and cyclooctyl. Polycyclic cycloalkyl radicals include, for example, adamantyl, norbornyl, decalinyl, 7,7-dimethyl-bicyclo[2.2.1]heptanyl, and the like. Unless otherwise stated specifically in the specification, a cycloalkyl group can be optionally substituted.

[0041] "Cycloalkenyl" refers to a stable non-aromatic monocyclic or polycyclic hydrocarbon radical consisting solely of carbon and hydrogen atoms, having one or more carbon-carbon double bonds, which can include fused or bridged ring systems, having from three to twenty carbon atoms, preferably having from three to ten carbon atoms, and which is attached to the rest of the molecule by a single bond. Monocyclic cycloalkenyl radicals include, for example, cyclopentenyl, cyclohexenyl, cycloheptenyl, cyclooctenyl, and the like. Polycyclic cycloalkenyl radicals include, for example, bicyclo[2.2.1]hept-2-enyl and the like. Unless otherwise stated specifically in the specification, a cycloalkenyl group can be optionally substituted.

[0042] "Cycloalkynyl" refers to a stable non-aromatic monocyclic or polycyclic hydrocarbon radical consisting solely of carbon and hydrogen atoms, having one or more carbon-carbon triple bonds, which can include fused or bridged ring systems, having from three to twenty carbon atoms, preferably having from three to ten carbon atoms, and which is attached to the rest of the molecule by a single bond. Monocyclic cycloalkynyl radicals include, for example, cycloheptynyl, cyclooctynyl, and the like. Unless otherwise stated specifically in the specification, a cycloalkynyl group can be optionally substituted.

[0043] "Cycloalkylalkyl" refers to a radical of the formula $-R_b-R_d$ where R_b is an alkylene, alkenylene, or alkynylene group as defined above and R_d is a cycloalkyl, cycloalkenyl, cycloalkynyl radical as defined above. Unless stated otherwise specifically in the specification, a cycloalkylalkyl group can be optionally substituted.

[0044] "Haloalkyl" refers to an alkyl radical, as defined above, that is substituted by one or more halo radicals, as defined above, *e.g.*, trifluoromethyl, difluoromethyl, trichloromethyl, 2,2,2-trifluoroethyl, 1,2-difluoroethyl, 3-bromo-2-fluoropropyl, 1,2-dibromoethyl, and the like. Unless stated otherwise specifically in the specification, a haloalkyl group can be optionally substituted.

[0045] "Haloalkenyl" refers to an alkenyl radical, as defined above, that is substituted by one or more halo radicals, as defined above, *e.g.*, 1-fluoropropenyl, 1,1-difluorobutenyl, and the like. Unless stated otherwise specifically in the specification, a haloalkenyl group can be optionally substituted.

[0046] "Haloalkynyl" refers to an alkynyl radical, as defined above, that is substituted by one or more halo radicals, as defined above, *e.g.*, 1-fluoropropynyl, 1-fluorobutynyl, and the like. Unless stated otherwise specifically in the specification, a haloalkenyl group can be optionally substituted.

[0047] "Heterocyclyl," "heterocyclic ring" or "heterocycle" refers to a stable 3- to 20-membered non-aromatic ring radical which consists of two to twelve carbon atoms and from one to six heteroatoms selected from the group consisting of nitrogen, oxygen and sulfur. Heterocyclyl or heterocyclic rings include heteroaryls as defined below. Unless stated otherwise specifically in the specification, the heterocyclyl radical can be a monocyclic, bicyclic, tricyclic or tetracyclic ring system, which can include fused or bridged ring systems; and the nitrogen, carbon or sulfur atoms in the heterocyclyl radical can be optionally oxidized; the nitrogen atom can be optionally quaternized; and the heterocyclyl radical can be partially or fully saturated. Examples of such heterocyclyl radicals include, but are not limited to, dioxolanyl, thienyl[1,3]dithianyl, decahydroisoquinolyl, imidazolinyl, imidazolidinyl, isothiazolidinyl, isoxazolidinyl, morpholinyl, octahydroindolyl, octahydroisoindolyl, 2-oxopiperazinyl, 2-oxopiperidinyl, 2-oxopyrrolidinyl, oxazolidinyl, piperidinyl, piperazinyl, 4-piperidonyl, pyrrolidinyl, pyrazolidinyl, quinuclidinyl, thiazolidinyl, tetrahydrofuryl, trithianyl, tetrahydropyranyl, thiomorpholinyl, thiamorpholinyl, 1-oxo-thiomorpholinyl, and 1,1-dioxo-thiomorpholinyl. Unless stated otherwise specifically in the specification, a heterocyclyl group can be optionally substituted.

[0048] "*N*-heterocyclyl" refers to a heterocyclyl radical as defined above containing at least one nitrogen and where the point of attachment of the heterocyclyl radical to the rest of the molecule is through a nitrogen atom in the heterocyclyl radical. Unless stated otherwise specifically in the specification, a *N*-heterocyclyl group can be optionally substituted.

[0049] "Heterocyclylalkyl" refers to a radical of the formula $-R_b-R_e$ where R_b is an alkylene, alkenylene, or alkynylene chain as defined above and R_e is a heterocyclyl radical as defined above, and if the heterocyclyl is a nitrogen-containing heterocyclyl, the heterocyclyl can be attached to the alkyl, alkenyl, alkynyl radical at the nitrogen atom. Unless stated otherwise specifically in the specification, a heterocyclylalkyl group can be optionally substituted.

[0050] "Heteroaryl" refers to a 5- to 20-membered ring system radical comprising hydrogen atoms, one to thirteen carbon atoms, one to six heteroatoms selected from the group consisting of nitrogen, oxygen and sulfur, and at least one aromatic ring. For purposes of this invention, the heteroaryl radical can be a monocyclic, bicyclic, tricyclic or tetracyclic ring system, which can include fused or bridged ring systems; and the nitrogen, carbon or sulfur atoms in the heteroaryl radical can be optionally oxidized; the nitrogen atom can be optionally quaternized. Examples include, but are not limited to, azepinyl, acridinyl, benzimidazolyl, benzothiazolyl, benzindolyl, benzodioxolyl, benzofuranyl, benzooxazolyl, benzothiazolyl, benzothiadiazolyl,

benzo[*b*][1,4]dioxepinyl, 1,4-benzodioxanyl, benzonaphthofuranyl, benzoxazolyl, benzodioxolyl, benzodioxinyl, benzopyranyl, benzopyranonyl, benzofuranyl, benzofuranonyl, benzothienyl (benzothiophenyl), benzotriazolyl, benzo[4,6]imidazo[1,2-a]pyridinyl, carbazolyl, cinnolinyl, dibenzofuranyl, dibenzothiophenyl, furanyl, furanonyl, isothiazolyl, imidazolyl, indazolyl, indolyl, indazolyl, isoindolyl, indolinyl, isoindolinyl, isoquinolyl, indolizinyl, isoxazolyl, naphthyridinyl, oxadiazolyl, 2-oxoazepinyl, oxazolyl, oxiranyl, 1-oxidopyridinyl, 1-oxidopyrimidinyl, 1-oxidopyrazinyl, 1-oxidopyridazinyl, 1-phenyl-1*H*-pyrrolyl, phenazinyl, phenothiazinyl, phenoxazinyl, phthalazinyl, pteridinyl, purinyl, pyrrolyl, pyrazolyl, pyridinyl, pyrazinyl, pyrimidinyl, pyridazinyl, quinazolinyl, quinoxalinyl, quinolinyl, quinuclidinyl, isoquinolinyl, tetrahydroquinolinyl, thiazolyl, thiadiazolyl, triazolyl, tetrazolyl, triazinyl, and thiophenyl (i.e. thienyl). Unless stated otherwise specifically in this disclosure, a heteroaryl group can be optionally substituted.

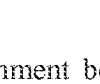
[0051] "*N*-heteroaryl" refers to a heteroaryl radical as defined above containing at least one nitrogen and where the point of attachment of the heteroaryl radical to the rest of the molecule is through a nitrogen atom in the heteroaryl radical. Unless stated otherwise specifically in the specification, an *N*-heteroaryl group can be optionally substituted.

[0052] "Heteroarylalkyl" refers to a radical of the formula $-R_b-R_f$ where R_b is an alkylene, alkenylene, or alkynylene chain as defined above and R_f is a heteroaryl radical as defined above. Unless stated otherwise specifically in the specification, a heteroarylalkyl group can be optionally substituted.

[0053] "Thioalkyl" refers to a radical of the formula $-SR_a$ where R_a is an alkyl, alkenyl, or alkynyl radical as defined above containing one to twelve carbon atoms. Unless stated otherwise specifically in the specification, a thioalkyl group can be optionally substituted.

[0054] The term "substituted" used herein means any of the above groups (*i.e.*, alkyl, alkylene, alkenyl, alkenylene, alkynyl, alkynylene, alkoxy, alkylamino, alkylcarbonyl, thioalkyl, aryl, aralkyl, carbocyclyl, cycloalkyl, cycloalkenyl, cycloalkynyl, cycloalkylalkyl, haloalkyl, heterocyclyl, *N*-heterocyclyl, heterocyclylalkyl, heteroaryl, *N*-heteroaryl and/or heteroarylalkyl) wherein at least one hydrogen atom is replaced by a bond to a non-hydrogen atoms such as, but not limited to: a halogen atom such as F, Cl, Br, and I; an oxygen atom in groups such as hydroxyl groups, alkoxy groups, and ester groups; a sulfur atom in groups such as thiol groups, thioalkyl groups, sulfone groups, sulfonyl groups, and sulfoxide groups; a nitrogen atom in groups such as amines, amides, alkylamines, dialkylamines, arylamines, alkylarylamines, diarylamines, N-oxides, imides, and enamines; a silicon atom in groups such as trialkylsilyl

groups, dialkylarylsilyl groups, alkyldiarylsilyl groups, and triarylsilyl groups; and other heteroatoms in various other groups. "Substituted" also means any of the above groups in which one or more hydrogen atoms are replaced by a higher-order bond (e.g., a double- or triple-bond) to a heteroatom such as oxygen in oxo, carbonyl, carboxyl, and ester groups; and nitrogen in groups such as imines, oximes, hydrazones, and nitriles. For example, "substituted" includes any of the above groups in which one or more hydrogen atoms are replaced with $-NR_gC(=O)OR_h$, $-NR_gSO_2R_h$, $-OC(=O)NR_gR_h$, $-OR_g$, $-SR_g$, $-SOR_g$, $-SO_2R_g$, $-OSO_2R_g$, $-SO_2OR_g$, $=NSO_2R_g$, and $-SO_2NR_gR_h$. "Substituted also means any of the above groups in which one or more hydrogen atoms are replaced with $-C(=O)R_g$, $-C(=O)OR_g$, $-C(=O)NR_gR_h$, $-CH_2SO_2R_g$, $-CH_2SO_2NR_gR_h$. In the foregoing, R_g and R_h are the same or different and independently hydrogen, alkyl, alkenyl, alkynyl, alkoxy, alkylamino, thioalkyl, aryl, aralkyl, cycloalkyl, cycloalkenyl, cycloalkynyl, cycloalkylalkyl, haloalkyl, haloalkenyl, haloalkynyl, heterocyclyl, *N*-heterocyclyl, heterocyclylalkyl, heteroaryl, *N*-heteroaryl and/or heteroarylalkyl. "Substituted" further means any of the above groups in which one or more hydrogen atoms are replaced by a bond to an amino, cyano, hydroxyl, imino, nitro, oxo, thioxo, halo, alkyl, alkenyl, alkynyl, alkoxy, alkylamino, thioalkyl, aryl, aralkyl, cycloalkyl, cycloalkenyl, cycloalkynyl, cycloalkylalkyl, haloalkyl, haloalkenyl, haloalkynyl, heterocyclyl, *N*-heterocyclyl, heterocyclylalkyl, heteroaryl, *N*-heteroaryl and/or heteroarylalkyl group. In addition, each of the foregoing substituents can also be optionally substituted with one or more of the above substituents.

[0055] As used herein, the symbol "  " (hereinafter can be referred to as "a point of attachment bond") denotes a bond that is a point of attachment between two chemical entities, one of which is depicted as being attached to the point of attachment bond and the other of which is not depicted as being attached to the point of attachment bond. For example, "  " indicates that the chemical entity "XY" is bonded to another chemical entity via the point of attachment bond. Furthermore, the specific point of attachment to the non-depicted chemical entity can be specified by inference. For example, the compound CH_3-R^3, wherein R^3 is H or "  " infers that when R^3 is "XY", the point of attachment bond is the same bond as the bond by which R^3 is depicted as being bonded to CH_3.

[0056] "Fused" refers to any ring structure described herein which is fused to an existing ring structure in the compounds of the invention. When the fused ring is a heterocyclyl ring or a

heteroaryl ring, any carbon atom on the existing ring structure which becomes part of the fused heterocyclyl ring or the fused heteroaryl ring can be replaced with a nitrogen atom.

[0057] "Optional" or "optionally" means that the subsequently described event of circumstances can or cannot occur, and that the description includes instances where said event or circumstance occurs and instances in which it does not. For example, "optionally substituted aryl" means that the aryl radical can or cannot be substituted and that the description includes both substituted aryl radicals and aryl radicals having no substitution.

[0058] Total synthesis refers to the complete chemical synthesis of a complex molecule, typically a natural product or a structurally similar analog or derivative thereof, starting from commercially available precursor compounds. It is often desirable to perform total syntheses in a "convergent" manner, where efficiency and overall chemical yield are improved by synthesizing several complex individual components in stage one, followed by combination of the components in a subsequent stage to yield a more advanced compound or final product. While convergent synthetic methods are desirable, for complex molecular frameworks such as communesins generally, or (–)-communesins specifically, there can be many different possible convergent approaches. The success of any particular approach is highly unpredictable.

[0059] The compounds of the invention, or their pharmaceutically acceptable salts can contain one or more asymmetric centers and can thus give rise to enantiomers, diastereomers, and other stereoisomeric forms that can be defined, in terms of absolute stereochemistry, as (*R*)- or (*S*)- or, as (D)- or (L)- for amino acids. The present invention is meant to include all such possible isomers, as well as their racemic and optically pure forms whether or not they are specifically depicted herein. Optically active (+) and (-), (*R*)- and (*S*)-, or (D)- and (L)- isomers can be prepared using chiral synthons or chiral reagents, or resolved using conventional techniques, for example, chromatography and fractional crystallization. Conventional techniques for the preparation/isolation of individual enantiomers include chiral synthesis from a suitable optically pure precursor or resolution of the racemate (or the racemate of a salt or derivative) using, for example, chiral high pressure liquid chromatography (HPLC). When the compounds described herein contain olefinic double bonds or other centers of geometric asymmetry, and unless specified otherwise, it is intended that the compounds include both E and Z geometric isomers. Likewise, all tautomeric forms are also intended to be included.

[0060] A "stereoisomer" refers to a compound made up of the same atoms bonded by the same bonds but having different three-dimensional structures, which are not interchangeable. The present invention contemplates various stereoisomers and mixtures thereof and includes

"enantiomers", which refers to two stereoisomers whose molecules are nonsuperimposable mirror images of one another.

[0061] A "tautomer" refers to a proton shift from one atom of a molecule to another atom of the same molecule. The present invention includes tautomers of any said compounds.

[0062] "Pharmaceutically acceptable carrier, diluent or excipient" includes without limitation any adjuvant, carrier, excipient, glidant, sweetening agent, diluent, preservative, dye/colorant, flavor enhancer, surfactant, wetting agent, dispersing agent, suspending agent, stabilizer, isotonic agent, solvent, or emulsifier which has been approved by the United States Food and Drug Administration as being acceptable for use in humans or domestic animals.

[0063] "Pharmaceutically acceptable salt" includes both acid and base addition salts.

[0064] "Pharmaceutically acceptable acid addition salt" refers to those salts which retain the biological effectiveness and properties of the free bases, which are not biologically or otherwise undesirable, and which are formed with inorganic acids such as, but are not limited to, hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid, phosphoric acid and the like, and organic acids such as, but not limited to, acetic acid, 2,2-dichloroacetic acid, adipic acid, alginic acid, ascorbic acid, aspartic acid, benzenesulfonic acid, benzoic acid, 4-acetamidobenzoic acid, camphoric acid, camphor-10-sulfonic acid, capric acid, caproic acid, caprylic acid, carbonic acid, cinnamic acid, citric acid, cyclamic acid, dodecylsulfuric acid, ethane-1,2-disulfonic acid, ethanesulfonic acid, 2-hydroxyethanesulfonic acid, formic acid, fumaric acid, galactaric acid, gentisic acid, glucoheptonic acid, gluconic acid, glucuronic acid, glutamic acid, glutaric acid, 2-oxo-glutaric acid, glycerophosphoric acid, glycolic acid, hippuric acid, isobutyric acid, lactic acid, lactobionic acid, lauric acid, maleic acid, malic acid, malonic acid, mandelic acid, methanesulfonic acid, mucic acid, naphthalene-1,5-disulfonic acid, naphthalene-2-sulfonic acid, 1-hydroxy-2-naphthoic acid, nicotinic acid, oleic acid, orotic acid, oxalic acid, palmitic acid, pamoic acid, propionic acid, pyroglutamic acid, pyruvic acid, salicylic acid, 4-aminosalicylic acid, sebacic acid, stearic acid, succinic acid, tartaric acid, thiocyanic acid, *p*-toluenesulfonic acid, trifluoroacetic acid, undecylenic acid, and the like.

[0065] "Pharmaceutically acceptable base addition salt" refers to those salts which retain the biological effectiveness and properties of the free acids, which are not biologically or otherwise undesirable. These salts are prepared from addition of an inorganic base or an organic base to the free acid. Salts derived from inorganic bases include, but are not limited to, the sodium, potassium, lithium, ammonium, calcium, magnesium, iron, zinc, copper, manganese, aluminum salts and the like. Preferred inorganic salts are the ammonium, sodium, potassium, calcium, and

magnesium salts. Salts derived from organic bases include, but are not limited to, salts of primary, secondary, and tertiary amines, substituted amines including naturally occurring substituted amines, cyclic amines and basic ion exchange resins, such as ammonia, isopropylamine, trimethylamine, diethylamine, triethylamine, tripropylamine, diethanolamine, ethanolamine, deanol, 2-dimethylaminoethanol, 2-diethylaminoethanol, dicyclohexylamine, lysine, arginine, histidine, caffeine, procaine, hydrabamine, choline, betaine, benethamine, benzathine, ethylenediamine, glucosamine, methylglucamine, theobromine, triethanolamine, tromethamine, purines, piperazine, piperidine, *N*-ethylpiperidine, polyamine resins and the like. Particularly preferred organic bases are isopropylamine, diethylamine, ethanolamine, trimethylamine, dicyclohexylamine, choline and caffeine.

[0066] Crystallization is a method commonly used to isolate a reaction product, for example one of the compounds disclosed herein, in purified form. Often, crystallization produces a solvate of the compound of the invention. As used herein, the term "solvate" refers to an aggregate that comprises one or more molecules of a compound of the invention with one or more molecules of solvent, typically in co-crystallized form. The solvent can be water, in which case the solvate can be a hydrate. Alternatively, the solvent can be an organic solvent. Thus, the compounds of the present invention can exist as a hydrate, including a monohydrate, dihydrate, hemihydrate, sesquihydrate, trihydrate, tetrahydrate and the like, as well as the corresponding solvated forms. The compound of the invention can be true solvates, while in other cases, the compound of the invention can merely retain adventitious water or be a mixture of water plus some adventitious solvent.

[0067] The chemical naming protocol and structure diagrams used herein are a modified form of the I.U.P.A.C. nomenclature system, using the ACD/Name Version 9.07 software program, ChemDraw Ultra Version 11.0.1 and/or ChemDraw Ultra Version 14.0 and/or ChemDraw Professional 16.0.0.82 software naming program (CambridgeSoft), or the like. For complex chemical names employed herein, a substituent group is named before the group to which it attaches. For example, cyclopropylethyl comprises an ethyl backbone with cyclopropyl substituent. Except as described below, all bonds are identified in the chemical structure diagrams herein, except for some carbon atoms, which are assumed to be bonded to sufficient hydrogen atoms to complete the valency.

[0068] The invention disclosed herein is also meant to encompass the *in vivo* metabolic products of the disclosed compounds. Such products can result from, for example, the oxidation, reduction, hydrolysis, amidation, esterification, and the like of the administered compound,

primarily due to enzymatic processes. Accordingly, the invention includes compounds produced by a process comprising administering a compound of this invention to a mammal for a period of time sufficient to yield a metabolic product thereof. Such products are typically identified by administering a radiolabeled compound of the invention in a detectable dose to an animal, such as rat, mouse, guinea pig, monkey, or to human, allowing sufficient time for metabolism to occur, and isolating its conversion products from the urine, blood or other biological samples.

[0069] "Stable compound" and "stable structure" are meant to indicate a compound that is sufficiently robust to survive isolation to a useful degree of purity from a reaction mixture, and formulation into an efficacious therapeutic agent.

[0070] As used herein, a "subject" can be a human, non-human primate, mammal, rat, mouse, cow, horse, pig, sheep, goat, dog, cat, insect and the like. The subject can be suspected of having or at risk for having a cancer, such as a blood cancer, or another disease or condition. Diagnostic methods for various cancers, and the clinical delineation of cancer, are known to those of ordinary skill in the art. The subject can also be suspected of having an infection or abnormal cardiovascular function.

[0071] "Mammal" includes humans and both domestic animals such as laboratory animals and household pets (*e.g.*, cats, dogs, swine, cattle, sheep, goats, horses, rabbits), and non-domestic animals such as wildlife and the like.

[0072] A "pharmaceutical composition" refers to a formulation of a compound of the invention and a medium generally accepted in the art for the delivery of the biologically active compound to mammals, *e.g.*, humans. Such a medium includes all pharmaceutically acceptable carriers, diluents or excipients therefor.

[0073] "An "effective amount" refers to a therapeutically effective amount or a prophylactically effective amount. A "therapeutically effective amount" refers to an amount effective, at dosages and for periods of time necessary, to achieve the desired therapeutic result, such as reduced tumor size, increased life span or increased life expectancy. A therapeutically effective amount of a compound can vary according to factors such as the disease state, age, sex, and weight of the subject, and the ability of the compound to elicit a desired response in the subject. Dosage regimens can be adjusted to provide the optimum therapeutic response. A therapeutically effective amount is also one in which any toxic or detrimental effects of the compound are outweighed by the therapeutically beneficial effects. A "prophylactically effective amount" refers to an amount effective, at dosages and for periods of time necessary, to achieve the desired prophylactic result, such as smaller tumors, increased life span, increased life

expectancy or prevention of the progression of prostate cancer to a castration-resistant form. Typically, a prophylactic dose is used in subjects prior to or at an earlier stage of disease, so that a prophylactically effective amount can be less than a therapeutically effective amount.

[0074] "Treating" or "treatment" as used herein covers the treatment of the disease or condition of interest in a mammal, preferably a human, having the disease or condition of interest, and includes (but is not limited to):

1. preventing the disease or condition from occurring in a mammal, in particular, when such mammal is predisposed to the condition but has not yet been diagnosed as having it;

2. inhibiting the disease or condition, i.e., arresting its development;

3. relieving the disease or condition, i.e., causing regression of the disease or condition (ranging from reducing the severity of the disease or condition to curing the disease of condition); or

4. relieving the symptoms resulting from the disease or condition, i.e., relieving pain without addressing the underlying disease or condition. As used herein, the terms "disease" and "condition" can be used interchangeably or can be different in that the particular malady or condition cannot have a known causative agent (so that etiology has not yet been worked out) and it is therefore not yet recognized as a disease but only as an undesirable condition or syndrome, wherein a more or less specific set of symptoms have been identified by clinicians.

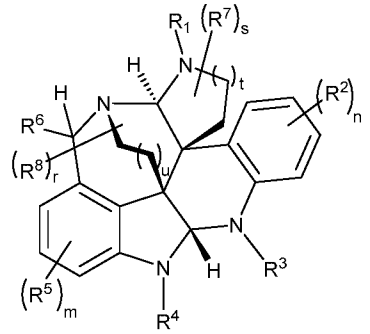
[0075] Throughout the present specification, the terms "about" and/or "approximately" can be used in conjunction with numerical values and/or ranges. The term "about" is understood to mean those values near to a recited value. For example, "about 40 [units]" can mean within ± 25% of 40 (*e.g.*, from 30 to 50), within ± 20%, ± 15%, ± 10%, ± 9%, ± 8%, ± 7%, ± 6%, ± 5%, ± 4%, ± 3%, ± 2%, ± 1%, less than ± 1%, or any other value or range of values therein or therebelow. Furthermore, the phrases "less than about [a value]" or "greater than about [a value]" should be understood in view of the definition of the term "about" provided herein. The terms "about" and "approximately" can be used interchangeably.

[0076] Throughout the present specification, numerical ranges are provided for certain quantities. It is to be understood that these ranges comprise all subranges therein. Thus, the range "from 50 to 80" includes all possible ranges therein (*e.g.*, 51-79, 52-78, 53-77, 54-76, 55-

75, 60-70, *etc.*). Furthermore, all values within a given range can be an endpoint for the range encompassed thereby (*e.g.*, the range 50-80 includes the ranges with endpoints such as 55-80, 50-75, *etc.*).

[0077] Following below are more detailed descriptions of various concepts related to, and embodiments of, inventive methods for Convergent and Biomimetic Enantioselective Total Synthesis of (–)-Communesin F. It should be appreciated that various concepts introduced above and discussed in greater detail below may be implemented in any of numerous ways, as the disclosed concepts are not limited to any particular manner of implementation. Examples of specific implementations and applications are provided primarily for illustrative purposes.

[0078] In one embodiment, the present disclosure relates to compounds of Formula (I):



Formula (I)

or a pharmaceutically acceptable salt, tautomer or stereoisomer thereof is described, wherein:

R^1, R^3, and R^4 are each independently selected from H, C_1-C_{12} alkyl, C_2-C_{12} alkenyl, C_2-C_{12} alkynyl, -C(=O)R^9, -C(=O)NR^9R^{10}, -S(=O)$_u$$R^{12}$, aryl, heteroaryl, carbocyclyl, or heterocyclyl, wherein R^3 and R^4 taken together with the carbon atoms to which they are attached form an aryl, heteroaryl, carbocyclic, or heterocyclic ring;

R^2 and R^5 are each independently selected from F, Cl, Br, I, -OH, -OR^9, -OC(=O)R^9, -S(=O)$_u$$R^{12}$, -N$R^9R^{10}$, C_1-C_{12} alkyl, C_2-C_{12} alkenyl, C_2-C_{12} alkynyl, aryl, heteroaryl, carbocyclyl, or heterocyclyl;

R^6 is independently H, -OH, -OR^9, -OC(=O)R^9, -S(=O)$_u$$R^{12}$, -N$R^9R^{10}$, C_1-C_{12} alkyl, C_1-C_{12} alkyl, C_2-C_{12} alkenyl, C_2-C_{12} alkynyl aryl, heteroaryl, carbocyclyl, or heterocyclyl;

R^7 and R^8 are each independently selected from H, C_1-C_{12} alkyl; C_2-C_{12} alkenyl, C_2-C_{12} alkynyl, -C(=O)R^9, -C(=O)NR^9R^{10}, -S(=O)$_u$$R^{12}$, -OH, -O$R^9$, -OC(=O)$R^9$, -N$R^9R^{10}$, aryl, heteroaryl, carbocyclyl, or heterocyclyl, wherein two R^7 or two R^8 groups taken together with the carbon atoms to which they are attached form an aryl, heteroaryl, carbocyclic, or heterocyclic

ring;

R^9 and R^{10} are each independently selected from H, C_1-C_{12} alkyl, C_2-C_{12} alkenyl, C_2-C_{12} alkynyl, aryl, heteroaryl, carbocyclyl, or heterocyclyl, wherein R^9 and R^{10} taken together with the carbon atoms to which they are attached form an aryl, heteroaryl, carbocyclic, or heterocyclic ring;

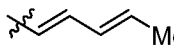
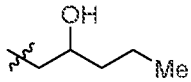
R^{12} is C_1-C_{12} alkyl, C_2-C_{12} alkenyl, C_2-C_{12} alkynyl, aryl, heteroaryl, carbocyclyl, heterocyclyl, $-(CH_2)_nSiMe_3$, $-(CH_2)_nR^9$;

m and t are each independently an integer from 0 to 3;

n, r, s, and v are each independently an integer from 0 to 4; and

u is 0, 1, or 2;

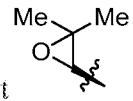
with the following provisos:

when R^1 is  , wherein R^{11} is Me, Et, *n*-Pr,  , or ; 

R^4 is Me;

m, n, r, and s are 0;

t and u are 1; then

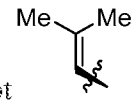
R^6 is not  ; and

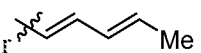
when R^1 is  , wherein R^{11} is Me;

R^4 is Me;

m, n, r, and s are 0;

t and u are 1; then

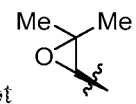
R^6 is not  ; and

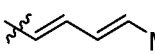
when R^1 is  , wherein R^{11} is Me, or  ;

R^4 is H;

m, n, r, and s are 0;

t and u are 1; then

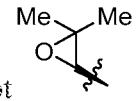
R^6 is not  ; and

when R^1 is  , wherein R^{11} is  ;

R^4 is -CHO;

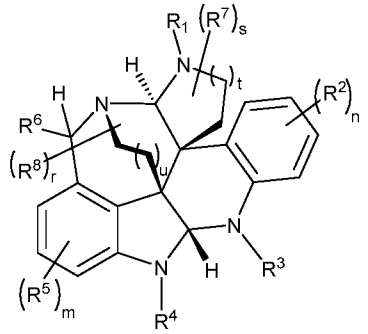
m, n, r, and s are 0;

t and u are 1; and

R^6 is not 

.

[0079] In another embodiment, the present disclosure relates to compounds of Formula (I):



Formula (I)

or a pharmaceutically acceptable salt, tautomer or stereoisomer thereof is described, wherein:

R^1, R^3, and R^4 are each independently selected from H, C_1-C_{12} alkyl, C_2-C_{12} alkenyl, C_2-C_{12} alkynyl, -C(=O)R^9, -C(=O)NR^9R^{10}, -S(=O)$_u$$R^{12}$, aryl, heteroaryl, carbocyclyl, or heterocyclyl, wherein R^3 and R^4 taken together with the carbon atoms to which they are attached form an aryl, heteroaryl, carbocyclic, or heterocyclic ring;

R^2 and R^5 are each independently selected from F, Cl, Br, I, -OH, -OR^9, -OC(=O)R^9, -S(=O)$_u$$R^{12}$, -N$R^9R^{10}$, C_1-C_{12} alkyl, C_2-C_{12} alkenyl, C_2-C_{12} alkynyl, aryl, heteroaryl, carbocyclyl, or heterocyclyl;

R^6 is independently H, -OH, -OR^9, -OC(=O)R^9, -S(=O)$_u$$R^{12}$, -N$R^9R^{10}$, C_1-C_{12} alkyl, C_1-C_{12} alkyl, C_2-C_{12} alkenyl, C_2-C_{12} alkynyl aryl, heteroaryl, carbocyclyl, or heterocyclyl;

R^7 and R^8 are each independently selected from H, C_1-C_{12} alkyl; C_2-C_{12} alkenyl, C_2-C_{12} alkynyl, -C(=O)R^9, -C(=O)NR^9R^{10}, -S(=O)$_u$$R^{12}$, -OH, -O$R^9$, -OC(=O)$R^9$, -N$R^9R^{10}$, aryl, heteroaryl, carbocyclyl, or heterocyclyl, wherein two R^7 or two R^8 groups taken together with the carbon atoms to which they are attached form an aryl, heteroaryl, carbocyclic, or heterocyclic ring;

R^9 and R^{10} are each independently selected from H, C_1-C_{12} alkyl, C_2-C_{12} alkenyl, C_2-C_{12} alkynyl, aryl, heteroaryl, carbocyclyl, or heterocyclyl, wherein R^9 and R^{10} taken together with the carbon atoms to which they are attached form an aryl, heteroaryl, carbocyclic, or heterocyclic ring;

R^{12} is C_1-C_{12} alkyl, C_2-C_{12} alkenyl, C_2-C_{12} alkynyl, aryl, heteroaryl, carbocyclyl,

heterocyclyl, $-(CH_2)_nSiMe_3$, $-(CH_2)_nR^9$;

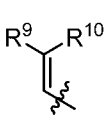
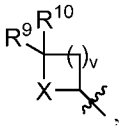
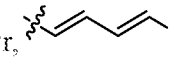
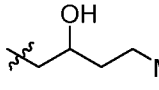
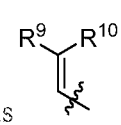
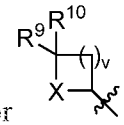
m and t are each independently an integer from 0 to 3;

n, r, s, and v are each independently an integer from 0 to 4; and

u is 0, 1, or 2;

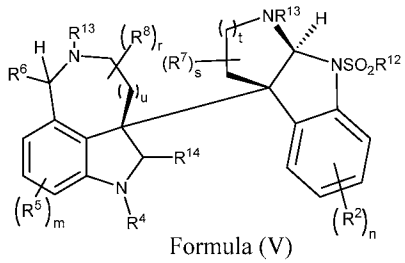
with the proviso that the compound of Formula (I) is not (–)-communesin A, (–)-communesin B, (–)-communesin C, (+)-communesin D, (–)-communesin E, (–)-communesin F, (–)-communesin G, or (–)-communesin H.

[0080] In various embodiments of Formula (I) compounds, R^6 is H, C_1-C_{12} alkyl, C_1-C_{12} alkenyl, aryl, heteroaryl, carbocyclyl, or heterocyclyl. In other embodiments, R^4 is H, $-C(=O)R^9$, C_1-C_{12} alkyl, aryl or heteroaryl. In some embodiments, R^3 is H, C_1-C_{12} alkyl, or $-S(=O)_uR^{12}$, wherein R^{12} is Ph or $-(CH)_2SiMe_3$. In other embodiments, R^2 and R^5 are each independently F, Br, Cl, I, C_1-C_{12} alkyl, aryl or heteroaryl.

[0081] In various other embodiments of Formula (I) compounds, R^6 is  , or  , and wherein X is O, NR^9, or $-S(=O)_uR^{12}$. In still other embodiments, R^1 is $-C(=O)R^9$. In some embodiments, R^9 of a $-C(=O)R^9$ group is Me, Et, *n*-Pr,  , or  . In various embodiments, R^6 is  , or  , wherein X is O, NR^9, or $-S(=O)_uR^{12}$.

[0082] In another embodiment, the present disclosure relates to a pharmaceutical composition comprising a compound of Formula (I) and a pharmaceutically acceptable excipient.

[0083] In one embodiment, the present disclosure relates to compounds of Formula (V):



Formula (V)

or a pharmaceutically acceptable salt, tautomer or stereoisomer thereof is described, wherein:

R^4 is independently selected from H, C_1-C_{12} alkyl, C_2-C_{12} alkenyl, C_2-C_{12} alkynyl, -C(=O)R^9, -C(=O)NR^9R^{10}, -S(=O)$_u$$R^{12}$, aryl, heteroaryl, carbocyclyl, or heterocyclyl, wherein R^3 and R^4 taken together with the carbon atoms to which they are attached form an aryl, heteroaryl, carbocyclic, or heterocyclic ring;

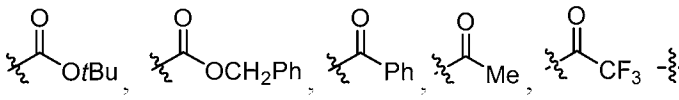
R^2 and R^5 are each independently selected from F, Cl, Br, I, -OH, -OR^9, -OC(=O)R^9, -S(=O)$_u$$R^{12}$, -$NR^9R^{10}$, C_1-C_{12} alkyl, C_2-C_{12} alkenyl, C_2-C_{12} alkynyl, aryl, heteroaryl, carbocyclyl, or heterocyclyl;

R^6 is independently H, -OH, -OR^9, -OC(=O)R^9, -S(=O)$_u$$R^{12}$, -$NR^9R^{10}$, C_1-C_{12} alkyl, C_1-C_{12} alkyl, C_2-C_{12} alkenyl, C_2-C_{12} alkynyl aryl, heteroaryl, carbocyclyl, or heterocyclyl;

R^7 and R^8 are each independently selected from H, C_1-C_{12} alkyl; C_2-C_{12} alkenyl, C_2-C_{12} alkynyl, -C(=O)R^9, -C(=O)NR^9R^{10}, -S(=O)$_u$$R^{12}$, -OH, -O$R^9$, -OC(=O)$R^9$, -$NR^9R^{10}$, aryl, heteroaryl, carbocyclyl, or heterocyclyl, wherein two R^7 or two R^8 groups taken together with the carbon atoms to which they are attached form an aryl, heteroaryl, carbocyclic, or heterocyclic ring;

R^9 and R^{10} are each independently selected from H, C_1-C_{12} alkyl, C_2-C_{12} alkenyl, C_2-C_{12} alkynyl, aryl, heteroaryl, carbocyclyl, or heterocyclyl, wherein R^9 and R^{10} taken together with the carbon atoms to which they are attached form an aryl, heteroaryl, carbocyclic, or heterocyclic ring;

R^{12} is C_1-C_{12} alkyl, C_2-C_{12} alkenyl, C_2-C_{12} alkynyl, aryl, heteroaryl, carbocyclyl, heterocyclyl, -$(CH_2)_n$$SiMe_3$, -$(CH_2)_n$$R^9$;

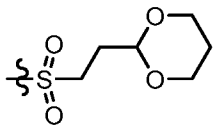
R^{13} is  ;

R^{14} is -OH, -OR^9, -NR^9R^{10}, S(O)$_u$$R^{12}$, or P(O)O$R^9$;

m and t are each independently an integer from 0 to 3;

n, r, s, and v are each independently an integer from 0 to 4; and

u is 0, 1, or 2.

[0084] In one embodiment, -S(=O)$_u$$R^{12}$ is  .

[0085] In one embodiment, the present disclosure provides a method of treating a disease or condition comprising administering an effective amount of a compound of Formula (I), or a pharmaceutical composition thereof to a subject. In one embodiment, the subject is a mammal. In another embodiment, the mammal is a human.

[0086] In some embodiments, the disease or condition being treated with a compound of Formula (I) is cancer. In other embodiments, the cancer is a cancer of the blood. In various other embodiments, the cancer of the blood to be treated can be selected from leukemias, lymphomas, Hodgkin's disease, myeloma, acute lymphocytic leukemia (ALL), acute myeloid leukemia (AML), acute promyelocytic leukemia (APL), chronic lymphocytic leukemia (CLL), chronic myeloid leukemia (CML), chronic neutrophilic leukemia (CNL), acute undifferentiated leukemia (AUL), anaplastic large-cell lymphoma (ALCL), prolymphocytic leukemia (PML), juvenile myelomonocytic leukemia (JMML), adult T-cell ALL, AML, with trilineage myelodysplasia (AMLITMDS), mixed lineage leukemia (MLL), myelodysplastic syndromes (MDSs), myeloproliferative disorders (MPD), and multiple myeloma (MM). In particular embodiments, the cancer of the blood is histiocytic leukemia, monocytic leukemia, Burkitt's lymphoma, Hodgkin's' lymphoma, T-cell leukemia, or B-cell leukemia.

[0087] Cancers of the blood, also termed hematologic cancers, begin in the blood forming tissue, such as bone marrow, or in cells of the immune system, and affects the production and function of blood cells. These abnormal blood cells, or cancerous cells, prevent the blood from performing many of its functions, like fighting off infections or preventing serious bleeding. Mutated forms can be resistant to currently available treatments, thus discovery and development of novel therapeutic agents is of critical importance.

[0088] In other embodiments, the disease or condition being treated with a compound of Formula (I), or pharmaceutical compositions thereof is a bacterial infection. Bacterial infections can be gram-positive or gram-negative with either type capable of high pathogenicity. In some embodiments, the treatment is for gram-positive infections. In other embodiments, the treatment is for gram-negative infections. In more specific embodiments, the bacterial infection treated is an infection of *Escherichia coli*, *Klebsiella pneumoniae*, *Pseudomonas aeruginosa*, *Acinetobacter baumanii*, *Neisseria gonorrhoeae*, or *Bacillus subtilis*.

[0089] Drug-resistant Gram-negative infections, such *as Klebsiella*, *Pseudomonas*, and *Acinetobacter*, have emerged as major concerns in hospitals, nursing homes, other healthcare settings, and more recently in the community. These types of infections disproportionately affect the very ill and the elderly, and often there are limited or no treatment options. The compounds of Formula (I) are suitable for treating such infections.

[0090] In other embodiments, the disease or condition being treated with a compound of Formula (I), or pharmaceutical compositions thereof is a fungal infection. In one embodiment, the fungal infections occur in subjects with a normal immune systems. In other embodiments,

the fungal infections occur in subjects with weakened immune systems. In other embodiments, the infection occurs on the skin, nails, genitals, esophagus, or other internal organs. In particular embodiments, the fungal infection treated with a compound of Formula (I) is a fungal infection of *Candida albicans*, *Trichophyton mentagrophytes*, or *Amorphotheca resinae*. In other embodiments, treatment of the fungal infections is by oral dosage or topical administration.

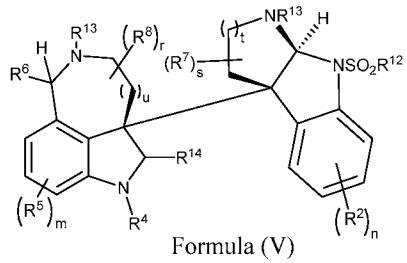
[0091] In another embodiment, the disease or condition being treated with a compound of Formula (I), or pharmaceutical compositions thereof is a viral infection. In one particular embodiment, the viral infection is *Herpes simplex* type 1.

[0092] In other embodiments, the disease or condition being treated with a compound of Formula (I), or pharmaceutical compositions thereof is abnormal cardiovascular function. In one embodiment, the abnormal cardiovascular function is bradycardia.

[0093] In yet another embodiment, insect infestations are treated with a compound of Formula (I), or an insecticidal composition thereof. In one specific embodiment, in the insect infestation to be treated is silkworms at the third instar larval stage. The third instar is a development stage of arthropod larvae characterized by changes in changes in body proportions, colors, patterns, number of body segments, and/or head width.

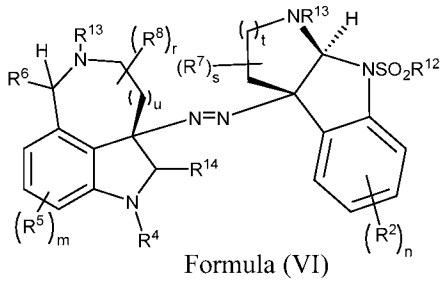
[0094] In various embodiments, the present disclosure is directed to synthetic methods including the expedient diazene–directed assembly of two advanced fragments described herein, to secure the congested C3a–C3a' linkage of the communesin framework in three steps, followed by a highly efficient aminal reorganization to access the heptacyclic communesin core in only two additional steps. Enantioselective syntheses of the two fragments were developed, with highlights including the catalytic asymmetric halocyclization and diastereoselective oxyamination reactions of tryptamine derivatives, a stereoselective sulfinimine allylation, and an efficient cyclotryptamine–C3a-sulfamate synthesis by either a new silver–promoted nucleophilic amination or a rhodium–catalyzed C–H amination protocol. The versatile synthesis of the fragments, their stereocontrolled assembly, and the efficient aminal–exchange as supported by in situ monitoring experiments, in addition to the final stage N1'-acylation of the communesin core provide a highly convergent synthesis of communesins.

[0095] In one embodiment, the present disclosure provides a method of making compounds of Formula (I) by a rearrangement of compounds of Formula (V):



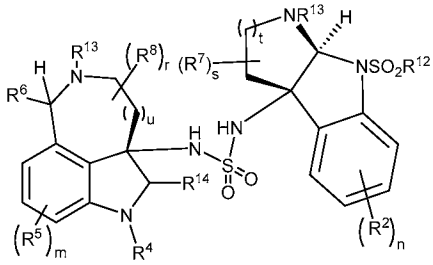
Formula (V)

[0096] In another embodiment, the present disclosure provides a method of making compounds of Formula (V) by a radical recombination reaction of Formula (VI):



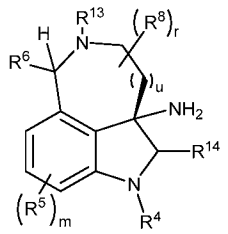
Formula (VI)

[0097] In another embodiment, the present disclosure provides a method of making compounds of Formula (VI) by the extrusion of sulfur from compounds of Formula (VII):

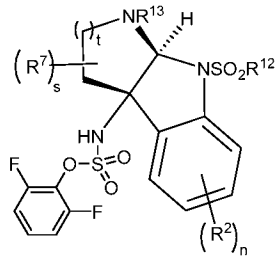


Formula (VII)

[0098] In still another embodiment, the present disclosure provides a method of making compounds of Formula (VII) by a nucleophilic substitution reaction between a compound of Formula (III) and a compound of Formula (VIII):

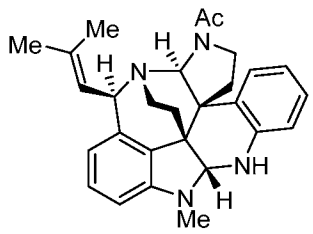


Formula (III)



Formula (VIII)

[0099] In one embodiment, the first biomimetic enantioselective total synthesis of (-)-communesin F based on a late-stage heterodimerization and aminal exchange is provided. It is to be understood that these methods and approaches can be generalized and applied to the synthesis of a variety of compounds, such as those represented by Formula (I).



(–)-communesin F

[00100] In various embodiments, the pharmaceutical compositions of the present disclosure can be formulated for administration by a variety of means including orally, parenterally, by inhalation spray, topically, or rectally in formulations containing pharmaceutically acceptable carriers, adjuvants and vehicles. The term parenteral as used here includes subcutaneous, intravenous, intramuscular, and intraarterial injections with a variety of infusion techniques. Intraarterial and intravenous injection as used herein includes administration through catheters.

[00101] The effective amount of a compound of Formula (I), pharmaceutically acceptable salts, esters, prodrugs, hydrates, solvates and isomers thereof, or a pharmaceutical composition comprising a compound of Formula (I) or a pharmaceutically acceptable salt thereof may be determined by one skilled in the art based on known methods.

[00102] In one embodiment, a pharmaceutical composition or a pharmaceutical formulation of the present disclosure comprises a compound of Formula (I) or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier, diluent, and/or excipient. Pharmaceutically acceptable carriers, diluents or excipients include without limitation any adjuvant, carrier, excipient, glidant, sweetening agent, diluent, preservative, dye/colorant, flavor enhancer, surfactant, wetting agent, dispersing agent, suspending agent, stabilizer, isotonic agent, solvent, or emulsifier which has been approved by the United States Food and Drug Administration as being acceptable for use in humans or domestic animals.

[00103] In one embodiment, suitable pharmaceutically acceptable carriers include, but are not limited to, inert solid fillers or diluents and sterile aqueous or organic solutions. Pharmaceutically acceptable carriers are well known to those skilled in the art and include, but are not limited to, from about 0.01 to about 0.1 M and preferably 0.05M phosphate buffer or

0.8% saline. Such pharmaceutically acceptable carriers can be aqueous or non-aqueous solutions, suspensions and emulsions. Examples of non-aqueous solvents suitable for use in the present application include, but are not limited to, propylene glycol, polyethylene glycol, vegetable oils such as olive oil, and injectable organic esters such as ethyl oleate.

[00104] Aqueous carriers suitable for use in the present application include, but are not limited to, water, ethanol, alcoholic/aqueous solutions, glycerol, emulsions or suspensions, including saline and buffered media. Oral carriers can be elixirs, syrups, capsules, tablets and the like.

[00105] Liquid carriers suitable for use in the present application can be used in preparing solutions, suspensions, emulsions, syrups, elixirs and pressurized compounds. The active ingredient can be dissolved or suspended in a pharmaceutically acceptable liquid carrier such as water, an organic solvent, a mixture of both or pharmaceutically acceptable oils or fats. The liquid carrier can contain other suitable pharmaceutical additives such as solubilizers, emulsifiers, buffers, preservatives, sweeteners, flavoring agents, suspending agents, thickening agents, colors, viscosity regulators, stabilizers or osmo-regulators.

[00106] Liquid carriers suitable for use in the present application include, but are not limited to, water (partially containing additives as above, e.g. cellulose derivatives, preferably sodium carboxymethyl cellulose solution), alcohols (including monohydric alcohols and polyhydric alcohols, e.g. glycols) and their derivatives, and oils (e.g. fractionated coconut oil and arachis oil). For parenteral administration, the carrier can also include an oily ester such as ethyl oleate and isopropyl myristate. Sterile liquid carriers are useful in sterile liquid form comprising compounds for parenteral administration. The liquid carrier for pressurized compounds disclosed herein can be halogenated hydrocarbon or other pharmaceutically acceptable propellant.

[00107] Solid carriers suitable for use in the present application include, but are not limited to, inert substances such as lactose, starch, glucose, methyl-cellulose, magnesium stearate, dicalcium phosphate, mannitol and the like. A solid carrier can further include one or more substances acting as flavoring agents, lubricants, solubilizers, suspending agents, fillers, glidants, compression aids, binders or tablet-disintegrating agents; it can also be an encapsulating material. In powders, the carrier can be a finely divided solid which is in admixture with the finely divided active compound. In tablets, the active compound is mixed with a carrier having the necessary compression properties in suitable proportions and compacted in the shape and size desired. The powders and tablets preferably contain up to 99% of the active compound. Suitable solid carriers include, for example, calcium phosphate, magnesium stearate, talc, sugars, lactose,

dextrin, starch, gelatin, cellulose, polyvinylpyrrolidine, low melting waxes and ion exchange resins. A tablet may be made by compression or molding, optionally with one or more accessory ingredients. Compressed tablets may be prepared by compressing in a suitable machine the active ingredient in a free flowing form such as a powder or granules, optionally mixed with a binder (e.g., povidone, gelatin, hydroxypropylmethyl cellulose), lubricant, inert diluent, preservative, disintegrant (e.g., sodium starch glycolate, cross-linked povidone, cross-linked sodium carboxymethyl cellulose) surface active or dispersing agent. Molded tablets may be made by molding in a suitable machine a mixture of the powdered compound moistened with an inert liquid diluent. The tablets may optionally be coated or scored and may be formulated so as to provide slow or controlled release of the active ingredient therein using, for example, hydroxypropyl methylcellulose in varying proportions to provide the desired release profile. Tablets may optionally be provided with an enteric coating, to provide release in parts of the gut other than the stomach.

[00108] Parenteral carriers suitable for use in the present application include, but are not limited to, sodium chloride solution, Ringer's dextrose, dextrose and sodium chloride, lactated Ringer's and fixed oils. Intravenous carriers include fluid and nutrient replenishers, electrolyte replenishers such as those based on Ringer's dextrose and the like. Preservatives and other additives can also be present, such as, for example, antimicrobials, antioxidants, chelating agents, inert gases and the like.

[00109] Carriers suitable for use in the present application can be mixed as needed with disintegrants, diluents, granulating agents, lubricants, binders and the like using conventional techniques known in the art. The carriers can also be sterilized using methods that do not deleteriously react with the compounds, as is generally known in the art.

[00110] Diluents may be added to the formulations of the present invention. Diluents increase the bulk of a solid pharmaceutical composition and/or combination, and may make a pharmaceutical dosage form containing the composition and/or combination easier for the patient and care giver to handle. Diluents for solid compositions and/or combinations include, for example, microcrystalline cellulose (e.g., AVICEL), microfine cellulose, lactose, starch, pregelatinized starch, calcium carbonate, calcium sulfate, sugar, dextrates, dextrin, dextrose, dibasic calcium phosphate dihydrate, tribasic calcium phosphate, kaolin, magnesium carbonate, magnesium oxide, maltodextrin, mannitol, polymethacrylates (e.g., EUDRAGIT(r)), potassium chloride, powdered cellulose, sodium chloride, sorbitol, and talc.

[00111] The pharmaceutical composition of the present invention may be prepared into any type of formulation and drug delivery system by using any of the conventional methods well-known in the art. The inventive pharmaceutical composition may be formulated into injectable formulations, which may be administered by routes including intrathecal, intraventricular, intravenous, intraperitoneal, intranasal, intraocular, intramuscular, subcutaneous or intraosseous. Also, it may also be administered orally, or parenterally through the rectum, the intestines or the mucous membrane in the nasal cavity (*see* Gennaro, A. R., ed. (1995) Remington's Pharmaceutical Sciences). Preferably, the composition is administered topically, instead of enterally. For instance, the composition may be injected, or delivered via a targeted drug delivery system such as a reservoir formulation or a sustained release formulation.

[00112] The pharmaceutical formulation of the present invention may be prepared by any well-known methods in the art, such as mixing, dissolving, granulating, dragee-making, levigating, emulsifying, encapsulating, entrapping, or lyophilizing processes. As mentioned above, the compositions of the present invention may include one or more physiologically acceptable carriers such as excipients and adjuvants that facilitate processing of active molecules into preparations for pharmaceutical use.

[00113] Proper formulation is dependent upon the route of administration chosen. For injection, for example, the composition may be formulated in an aqueous solution, preferably in physiologically compatible buffers such as Hank's solution, Ringer's solution, or physiological saline buffer. For transmucosal or nasal administration, penetrants appropriate to the barrier to be permeated are used in the formulation. Such penetrants are generally known in the art. In a one embodiment of the present invention, the inventive compound may be prepared in an oral formulation. For oral administration, the compounds can be formulated readily by combining the active compounds with pharmaceutically acceptable carriers known in the art. Such carriers enable the disclosed compound to be formulated as tablets, pills, dragees, capsules, liquids, gels, syrups, slurries, suspensions and the like, for oral ingestion by a subject. The compounds may also be formulated in rectal compositions such as suppositories or retention enemas, *e.g.*, containing conventional suppository bases such as cocoa butter or other glycerides.

[00114] Pharmaceutical preparations for oral use may be obtained as solid excipients, optionally grinding a resulting mixture, and processing the mixture of granules, after adding suitable adjuvants, if desired, to obtain tablets or dragee cores. Suitable excipients may be, in particular, fillers such as sugars, including lactose, sucrose, mannitol, or sorbitol; cellulose formulation such as maize starch, wheat starch, rice starch, potato starch, gelatin, gum

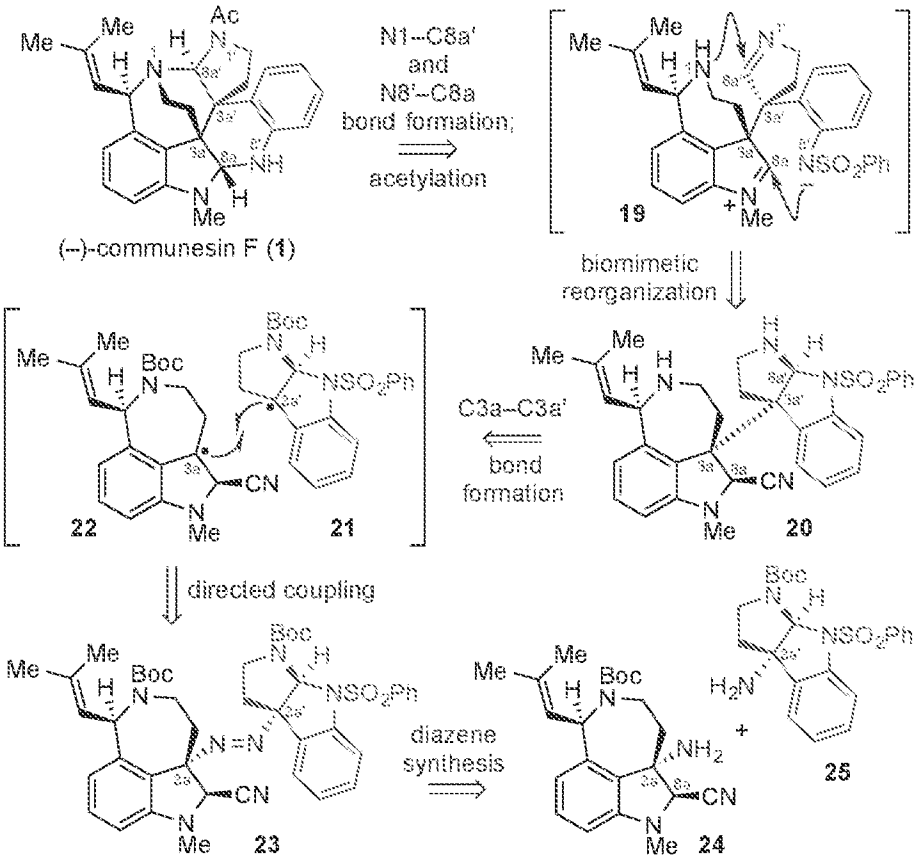
tragacanth, methyl cellulose, hydroxypropylmethyl-cellulose, sodium carboxymethylcellulose, and/or polyvinylpyrrolidone (PVP) formulation. Also, disintegrating agents may be employed, such as cross-linked polyvinylpyrrolidone, agar, or alginic acid or a salt thereof such as sodium alginate. Also, wetting agents, such as sodium dodecyl sulfate and the like, may be added.

[00115] Dragee cores are provided with suitable coatings. For this purpose, concentrated sugar solutions may be used, which may optionally contain gum arabic, talc, polyvinylpyrrolidone, carbopol gel, polyethylene glycol, and/or titanium dioxide, lacquer solutions, and suitable organic solvents or solvent mixtures. Dyestuffs or pigments may be added to the tablets or dragee coatings for identification or to characterize different combinations of active compounds doses.

[00116] The present disclosure is in various embodiments directed to a unified and convergent approach to the communesin alkaloids involving the stereocontrolled oxidative union of two dissimilar tryptamine derivatives followed by reorganization of a C3a–C3a' linked heterodimer, reminiscent of the pathways leading to the related calycanthoids (Scheme 1).

[00117] This method involves the directed and stereocontrolled union of two dissimilar fragments followed by selective reorganization of a C3a–C3a' linked heterodimer **19** to a single constitutional isomer consistent with the communesin skeleton (Scheme 2).

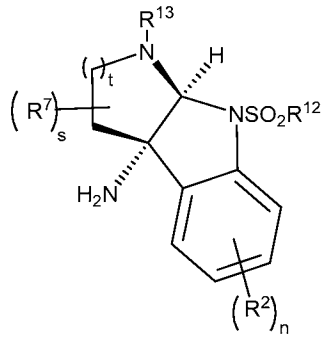
Scheme 2. Retrosynthetic Analysis of (–)-Communesin F (**1**)



[00118] As illustrated in the retrosynthetic analysis of (–)-communesin F (**1**, Scheme 2), one embodiment of the retrosynthetic design is focused on the efficient assembly and reorganization of a key heterodimeric intermediate **20**. We envisioned hexacycle **20** (Scheme 2) to serve as a surrogate for the intermediate **15** (Scheme 1). We anticipated the N8'-sulfonamide would guide the opening of the C8a'-aminal to present the C8a'-imine for N1-addition. Furthermore, we projected the ionization of the C8a-nitrile would offer the C8a-imininium ion needed for aminal formation via N8'-addition. The challenging C3a–C3a' linkage of heterodimer **20** required a directed and stereocontrolled union of a cyclotryptamine fragment **21** and aurantioclavine derivative **22** to simultaneously secure the two critical quaternary stereocenters. Our diazene-based strategy for directed complex fragment assembly provided the essential framework to explore this exciting and convergent approach to (–)-communesin F (**1**). While we believe the C8a'-stereochemisry of the cyclotryptamine moiety may guide the desired C3a'-stereochemical

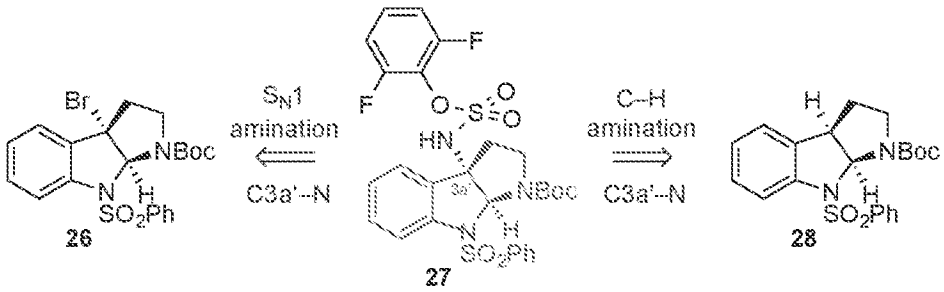
outcome in this union, the potential level of stereochemical control at C3a during carbon–carbon bond formation was not known. We envisioned the synthesis of complex heterodimeric diazene **23** from tricyclic amines **24** and **25** as tryptamine–surrogates necessary for securing the C3a–C3a' linkage (Scheme 2).

Formula (II) compounds, exemplified by tricyclic indoline **28** (Scheme 3), can be prepared according to the methods described herein and used for the synthesis of compounds of Formula (I), wherein R^2, R^7, R^{12}, R^{13}, n, s, and t are each defined herein. The general strategy and representative examples are highlighted in Schemes 3-5.



Formula (II)

Scheme 3. Strategies for Synthesis of Tricycle **28**

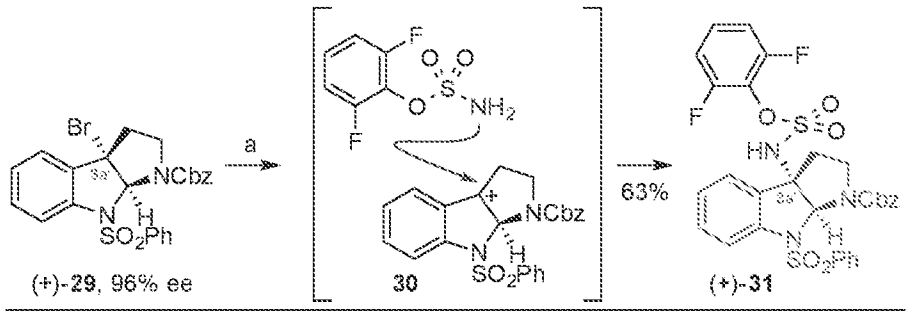


[00119] The synthesis of (–)-communesin F (**1**) commenced with the preparation of the two key tricyclic amines **24** and **25** required for the assembly of critical diazene **23** (Scheme 2). Two approaches to the synthesis of the C3a'-amino cyclotryptamine **25** and the corresponding sulfamate **27** (Scheme 3) were pursued. In the first approach, motivated by the potential for efficient access to enantiomerically enriched C3a'-halocyclotryptamine derivatives, a nucleophilic C3a'-amination (Scheme 4) was used. The second approach to amine **25** relied on Du Bois amination (Roizen, J. L.; Zalatan, D. N.; Du Bois, J. *Angew. Chem. Int. Ed.* **2013**, *52*, 11343) of cyclotryptamine **28** to secure the sulfamate **27** (Scheme 5).

[00120] One of skill in the art will appreciate that by selection of appropriately substituted starting materials, other cyclotryptamine compounds of Formula (II) can be prepared by analogous methods.

[00121] Given the versatility of cyclotryptamine–sulfamates as precursors to the corresponding mixed sulfamides, an efficient synthesis was developed to access sulfamate (+)-**31** and related derivatives starting with C3a'-bromo-cyclotryptamine (+)-**29** (Scheme 4). Enantioselective bromocyclization of *Nβ*-Cbz-*N1*-benzenesulfonyl-tryptamine catalyzed by (*S*)-3,3'-bis(2,4,6-triisopropyl-phenyl)-1,1'-binaphthyl-2,2'-diyl hydrogenphosphate (TRIP) afforded C3a'-bromocyclotryptamine (+)-**29** in 93% yield and 96% enantiomeric excess. Significantly, electrophilic activation of the tricyclic bromide (+)-**29** in the presence of 2,6-difluorophenylsulfamate provided the desired sulfamate (+)-**31** in 63% yield (Scheme 4). The use of 2,6-difluorophenylsulfamate as a nucleophile to trap an intermediate C3a'-electrophile **30** provides a new and expedient route for the directed synthesis of complex diazenes. While this new single-step synthesis of C3a'-sulfamates from the corresponding C3a'-bromides offers a concise solution to the desired precursors, its utility in conversion of the more acid sensitive *tert*-butyl carbamate substrate **26** to sulfamate **27** gave capricious and inferior outcomes (~50% yield).

Scheme 4. Concise Synthesis of Sulfamate (+)-**31**[a]

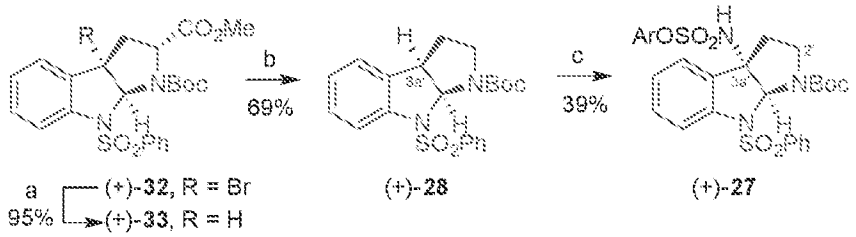


[a]Reagents and conditions: (a) $AgSbF_6$, 2,6-di-*tert*-butyl-4-methylpyridine, 2,6-difluorophenylsulfamate, CH_2Cl_2, 23 °C, 63%.

[00122] An alternate approach for the synthesis of *tert*-butyl-carbamate derivative **27** relied on the C–H amination chemistry illustrated in Scheme 5. Mild reduction of bromocyclotryptophan (+)-**32** provided the desired C3a'–H cyclotryptophan (+)-**33** in 95% yield. Subsequent decarboxylation furnished cyclotryptamine (+)-**28** in 69% yield. Under optimal conditions, a Rh-catalyzed C–H amination of cyclotryptamine (+)-**28** afforded the desired sulfamate (+)-**27** in 39% yield after recrystallization. This three-step sequence efficiently

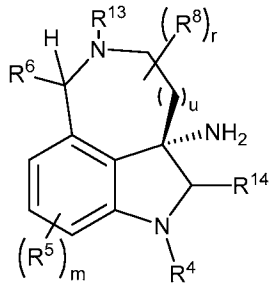
generated gram quantities of (+)-**27** from the readily available bromocyclotryptophan (+)-**32** as an activated form of C3a'-aminocyclotryptamine **25** (Scheme 2) that is ready for coupling with tricyclic amine **24** for diazene synthesis.

Scheme 5. Gram-scale Synthesis of Sulfamate (+)-27[a]



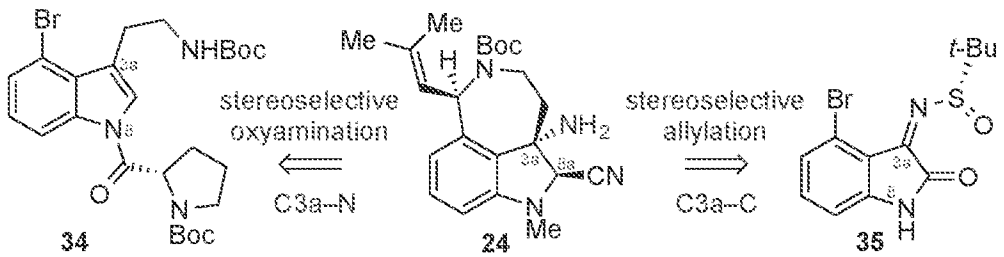
[a]Reagents and conditions: (a) $(Me_3Si)_3SiH$, Et_3B, air, 23 °C, >99:1 dr; (b) (i) KOH (aq.), MeOH, CH_2Cl_2, 23 °C, (ii) *N,N,N',N'*-tetramethylchloroformamidinium hexafluorophosphate, thiopyridine *N*-oxide, 4-(*N,N*-dimethylamino)pyridine, Et_3N, THF; *t*-BuSH, hν, 23 °C; (c) $Rh_2(esp)_2$, H_2NSO_3Ar, $PhI(OAc)_2$, $Ph(CH_3)_2CCO_2H$, MgO, 5Å-MS, *i*-PrOAc, 23 °C; Ar=2,6-difluorobenzene.

[00123] Compounds of Formula (III), exemplified by **24** (Scheme 6) can be prepared according to the methods described herein and used for the synthesis of compounds of Formula (I), wherein R_4, R^5, R^6, R^8, R^{13}, R^{14}, m, r, and u are each defined herein. The general strategy and representative examples are found in Schemes 6-8.



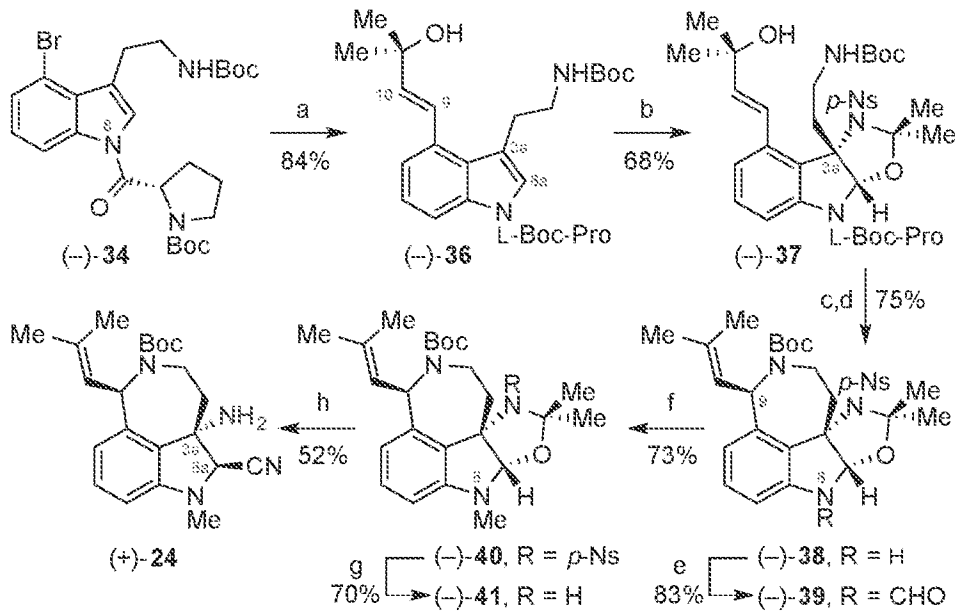
Formula (III)

Scheme 6. Strategies for Synthesis of Tricycle **24**



[00124] The synthesis of a derivative needed to mimic fragment **22**, necessary for the disclosed approach to (–)-communesin F (**1**), is not known. Accordingly, the present inventors developed an enantioselective synthesis of a tricyclic intermediate that would allow for implementation of our synthetic strategy (Scheme 2). The tricyclic aminonitrile **24** offered the necessary C3a-amine for diazene synthesis and the C2-aminonitrile to allow for mild generation of the corresponding C2-iminium ion needed for aminal synthesis. Two strategies were developed to access the key intermediate **24** as illustrated in Scheme 6. The first strategy involved tryptamine **34** as the substrate for the application of Yoon's oxyamination chemistry, while the second strategy utilized *tert*-butyl sulfinimine **35** and Ellman's asymmetric allylation of such substrates.

Scheme 7. Oxyamination Approach to Tricycle (+)-**24**[a]

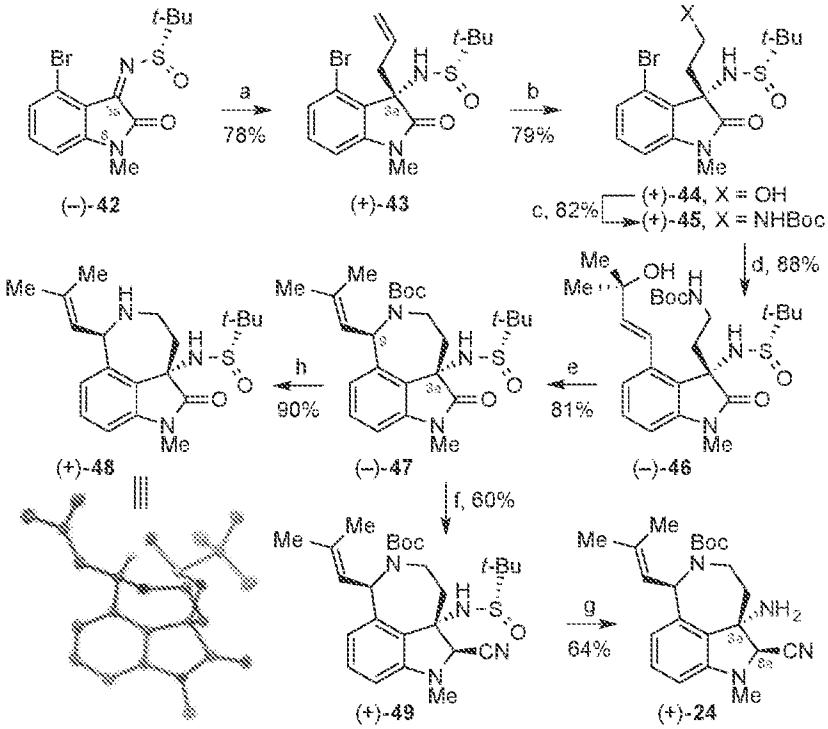


[a]Reagents and conditions: (a) 1,1-dimethylallyl alcohol, $Pd(OAc)_2$, P(*o*-tol)$_3$, Et_3N, MeCN, 95 °C; (b) 3,3-dimethyl-2-(*p*-nitrobenzenesulfonyl)-1,2-oxaziridine, $CuCl_2$, *n*-Bu_4NCl, $CHCl_3$, 21 °C, 89:11 dr; (c) $PdCl_2(MeCN)_2$, MeCN, 82 °C; (d) (i) *i*-Bu_2AlH, THF, 0 °C, (ii) 1,8-diazabicyclo[5.4.0]undec-7-ene, MeOH, 21 °C; (e) Ac_2O, HCO_2H, pyridine, CH_2Cl_2, 21 °C; (f) $NaBH_4$, TFA, THF, 0 °C; (g) PhSH, K_2CO_3, DMF, 50 °C; (h) Me_3SiCN, $(F_3C)_2CHOH$, H_2O, 21 °C; *p*-Ns = *para*-nitrobenzenesulfonyl.

[00125] The oxyamination route to aminonitrile **24** commenced with a Mizoroki-Heck reaction of bromoindole (–)-**34** with 1,1-dimethylallyl alcohol to provide allylic alcohol (–)-**36**. Despite early reservations regarding possible competing C9-C10-oxyamination of vinyl indole (–)-**36** in place of the desired C3a-C8a-oxyamination, higher levels of diastereoselection for the oxyamination of the more advanced substrate (–)-**36** (Scheme 7) were observed. The use of

stoichiometric copper(II) chloride facilitated the reaction and gave oxazoline (–)-**37** in 68% yield (89:11 dr). Treatment of alcohol (–)-**37** with bis(acetonitrile)dichloropalladium(II) in acetonitrile to form the desired azepane (85% yield) followed by removal of the chiral auxiliary (88% yield) provided the desired indoline (–)-**38**. The formylation of indoline (–)-**38** to give formamide (–)-**39** (83% yield) followed by mild reduction with sodium borohydride in the presence of trifluoroacetic acid gave the desired *N*-methylindoline (–)-**40** (73% yield). Exposure of sulfonamide (–)-**40** to thiophenol and potassium carbonate led to removal of the *para*-nitrobenzenesulfonyl group and the isolation of the stable oxazolidine (–)-**41** in 70% yield. Given the propensity of oxazolidine (–)-**41** and aminonitrile (+)-**24** toward elimination of the C3a-amino group under strongly acidic or basic conditions, we developed mild hydrolysis conditions to allow for cyanation of a transient C2-hemiaminal leading to aminonitrile (+)-**24** in 52% yield in addition to the C2-epimer (26%). While this approach provides flexibility for the late-stage introduction of various N8-substituents and establishes the C3a-stereochemistry, the challenge in unraveling the oxazolidine substructure prompted our investigation of an alternate route to aminonitrile (+)-**24** (Scheme 6) involving C3a-C bond formation.

Scheme 8. Sulfinimine Allylation Approach to Tricycle (+)-**24**[a]



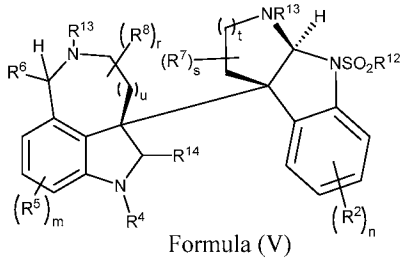
[a]Reagents and conditions: (a) allylMgBr, $MgBr_2$, CH_2Cl_2, –78 °C, >98:2 dr; (b) O_3, MeOH, –78 °C; $NaBH_4$, –78 → 23 °C; (c) *o*-NsNHBoc, diisopropyl azodicarboxylate, polystyrene–PPh_3, THF, 50 °C; PhSH, Cs_2CO_3, 50 °C; (d) $Me_2C(OH)CH{=}CHSn(n\text{-}Bu)_3$,

$PdCl_2(PPh_3)_2$, PhMe, THF, 110 °C; (e) $PdCl_2(MeCN)_2$, MeCN, 80 °C; (f) (i) $LiBH_4$, MeOH, THF, 0 → 23 °C; (ii) Me_3SiCN, $(F_3C)_2CHOH$, 0 °C; (g) HCl, dioxane, MeOH, 23 °C; (h) $Sc(OTf)_3$, F_3CCH_2OH, 23 °C; *o*-Ns = *ortho*-nitrobenzenesulfonyl. ORTEP representation of amine (+)-**48**: thermal ellipsoids drawn at 50% probability.

[00126] The alternative synthesis of aminonitrile (+)-**24** began with the diastereoselective allylation of N8-methyl sulfinimine (–)-**42** (Scheme 8) to provide allyl oxindole (+)-**43** in 78% yield and with excellent diastereopurity after trituration of the crude addition product with hexane (>98:2 dr). In contrast to the first approach to aminonitrile (+)-**24**, the placement of the chiral auxiliary on the C3a-substituent enabled the use of the N8-methyl variant of sulfinimine **35** (Scheme 6). Ozonolysis of alkene (+)-**43** followed by a reductive work-up afforded the primary alcohol (+)-**44** in 79% yield. The alcohol (+)-**44** was then converted to *tert*-butyl carbamate (+)-**45** in 82% yield via a Mitsunobu displacement and subsequent in situ desulfonylation. The allylic alcohol needed for synthesis of the azepane substructure was introduced via a Stille vinylation to furnish allylic alcohol (–)-**46** in 88% yield. A palladium-catalyzed allylic amination provided azepane (–)-**47** in 81% yield as a single diastereomer. The stereochemistry at C3a and C9 of azepane (–)-**47** was confirmed unambiguously through analysis of the crystal structure of the corresponding amine (+)-**48** (Scheme 8).

[00127] Conditions for the mild and efficient conversion of oxindole (–)-**47** to the desired aminonitrile (+)-**24** were then developed. Partial reduction of oxindole (–)-**47** with lithium borohydride afforded a mixture of C2-hemiaminal diastereomers that were too labile for isolation. Direct treatment of the crude hemiaminal with trimethylsilyl cyanide in hexafluoroisopropanol furnished the desired aminonitrile (+)-**49** in 60% yield and the easily separable minor C2-epimer (30%). Methanolysis of the *tert*-butyl sulfinamide (+)-**49** provided the desired amino-azepane (+)-**24** in 64% yield. The C2-aminonitrile proved to be an ideal trigger for late stage hemiaminal formation while providing adequate stability for the implementation of an efficient fragment assembly. We anticipate future adaptation of this robust synthetic route to other N8-variants of azepane (+)-**24** via judicious N8-substitution of sulfinimine **35**.

[00128] Compounds of Formula (V) represented by heterodimer (+)-**51** can be prepared according to the methods described herein, and used for the synthesis of compounds of Formula (I), wherein R^4, R^5, R^6, R^8, R^{12}, R^{13}, R^{14}, m, n, r, s, t and u are each defined herein.

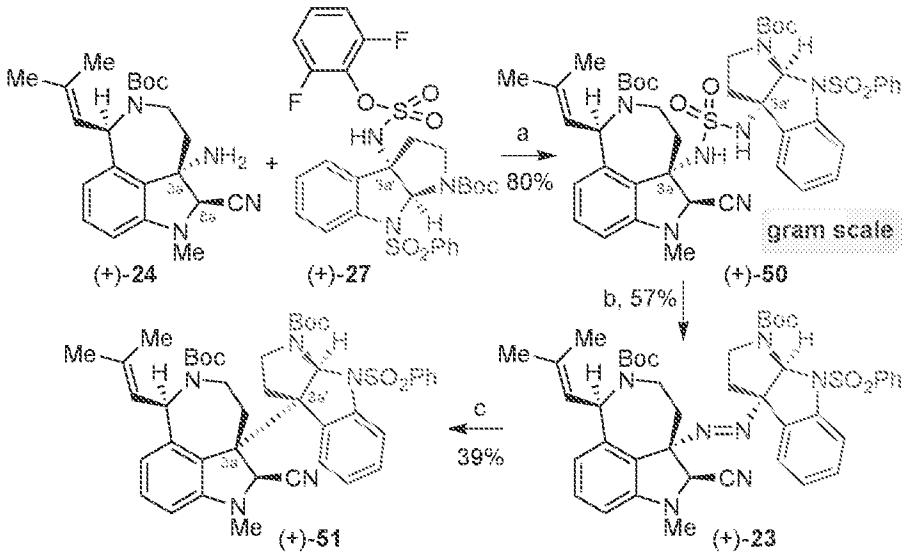


Formula (V)

Formula (V)

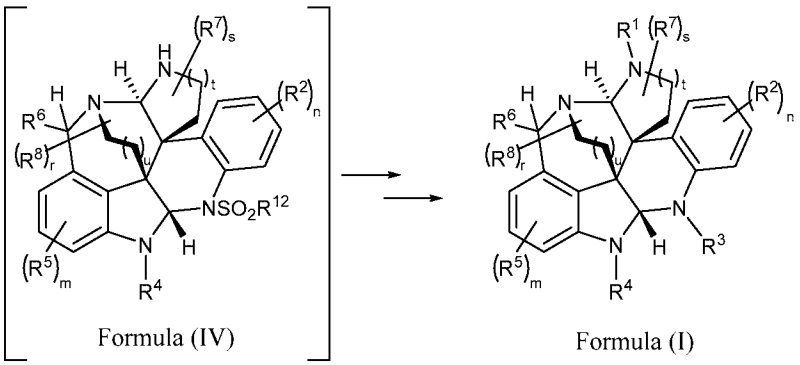
[00129] After developing versatile syntheses of both essential fragments, the union of azepane (+)-**24** and cyclotryptamine (+)-**27** was then examined to introduce the critical C3a–C3a' bond. Dissolution of the two fragments in tetrahydrofuran in the presence of 4-(*N*,*N*-dimethylamino)pyridine afforded sulfamide (+)-**50** in 80% yield on gram-scale (Scheme 9). The oxidation of sterically shielded sulfamides containing electron-rich arenes, such as the *N*-methyl aniline substructure of sulfamide (+)-**50**, suffers from competitive arene-halogenation. After extensive experimentation, the unique ability of tertiary *N*-chloroamides to affect chemoselective oxidation of sulfamide (+)-**50** to the corresponding diazene (Scheme 9) without competitive arene-halogenation was discovered. Exposure of sulfamide (+)-**50** to *N*-chloro-*N*-methylbenzamide (6 equiv) in conjunction with polystyrene-bound 2-*tert*-butylimino-2-diethylamino-1,3-dimethyl-perhydro-1,3,2-diazaphosphorine (BEMP) in methanol provided the desired diazene (+)-**23** in 57% yield. Photoexcitation and expulsion of dinitrogen from a thin film of diazene (+)-**23**, followed by radical combination of the resulting cyclotryptamine **21** and azepane **22** (Scheme 2), afforded the desired heterodimer (+)-**51** in 39% yield as a single diastereomer. The remarkable diastereoselection at C3a of heterodimer (+)-**51** is notable and may be due to the confluence of a rapid radical combination step and the additional stereoinduction imposed by the C2-nitrile. Importantly, this diazene-based strategy for directed complex fragment assembly allowed for the stereoselective construction of the critical C3a–C3a' linkage, securing the corresponding vicinal quaternary stereocenters.

Scheme 9. Directed Synthesis of Heterodimer (+)-**51**,[a]



[a]Reagents and conditions: (a) 4-(*N*,*N*-dimethylamino)pyridine, THF, 23 °C; (b) polystyrene–2-*t*-butylimino-2-diethylamino-1,3-dimethyl-perhydro-1,3,2-diazaphosphorine, *N*-chloro-*N*-methylbenzamide, MeOH, 23 °C; (c) hv (350 nm), 25 °C.

[00130] Transient intermediates of Formula (IV), represented by (–)-**52**, can be prepared according to the methods described herein and subsequently converted to compounds of Formula (I), wherein R^1-R^8, R^{12}, R^{13}, m, n, r, s, t, and u are each defined herein.

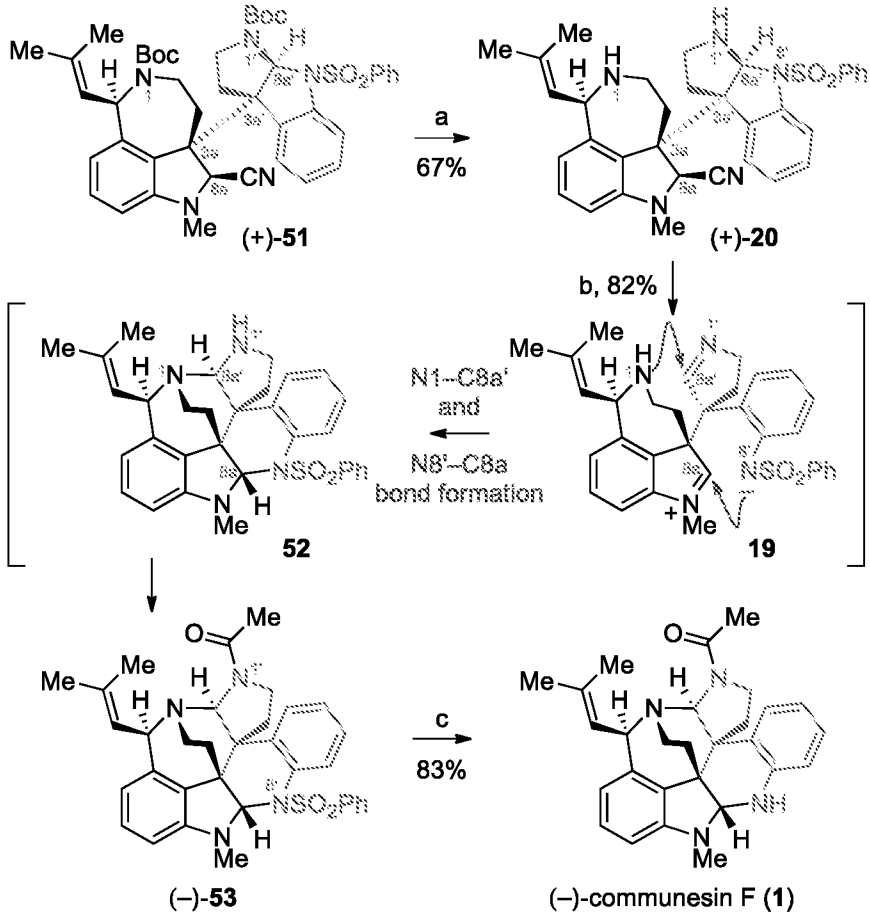


[00131] The reaction conditions for the planned transformation of (+)-**51** were carefully selected due to the sensitive nature of the C3a–C3a' linkage. It was thought that an appropriate sequence of amine unveiling would maximize efficiency for the desired aminal exchange, and that unveiling the N1- and N1'-amines of heterodimer (+)-**51** would allow opening of the C8a' aminal with the benzenesulfonamide as the leaving group, thus allowing rapid trapping of the C8a'-imine of intermediate **19** en route to heptacycle **52**.

[00132] Treatment of heterodimer (+)-**51** with scandium trifluoromethanesulfonate in trifluoroethanol provided the desired heterodimer (+)-**20** by selective removal of the *tert*-butyl

carbamates while preserving the sensitive C8a-aminonitrile (Scheme 10). The electron-withdrawing N8'-sulfonamide permitted an examination of basic conditions to selectively open the cyclotryptamine substructure. Treatment of heterodimer (+)-**20** with lithium *tert*-butoxide in methanol provided clean and complete conversion to the desired heptacyclic structure **52** within 1 h at 50° C as observed by in situ ^{1}H-NMR spectroscopy. Significantly, only the desired heptacycle **52** was formed in preference to other constitutional isomers. Methanol was found to be an excellent solvent for this transformation, possibly due to its ability to stabilize reactive intermediates as the corresponding *O*-alkyl-hemiaminals. It was found that other groups such as OH, OC_{1-4} alkyl (e.g., OMe) or $P(O)(OEt)_2$ can be used in place of C8a-CN, thereby improving flexibility. Although intermediate **52** could be observed by in situ ^{1}H NMR spectroscopy, this compound did not show sufficient stability for isolation. This may be due to the sensitive nature of the C8a'-aminal of heptacycle **52**, which upon reversible opening to the C8a'-imine increases the lability of the C3a–C3a' bond. As an indication of the sensitivity of the C3a–C3a' linkage of heterodimer (+)-**20**, simple heating of a derivative (C8a-OMe instead of C8a-CN) in acetonitrile-d_3 at 80 °C predominantly led to fragmentation. Treatment of the basic solution of heptacycle **52** with pyridinium *p*-toluenesulfonate to quench the alkoxides, followed by addition of acetic anhydride afforded the *N*1'-acetyl derivative (–)-**53** in 82% overall yield. A final-step unveiling of the N8'-amine was accomplished by treatment of (–)-**53** with sodium amalgam to provide (–)-communesin F (**1**) in 83% yield. All ^{1}H and ^{13}C NMR data as well as optical rotation (observed $[\alpha]_D^{24} = -249$, $c = 0.13$, $CHCl_3$; literature $[\alpha]_D^{20} = -264$, $c = 0.34$, $CHCl_3$), for our synthetic (–)-communesin F (**1**) were in agreement with literature data.

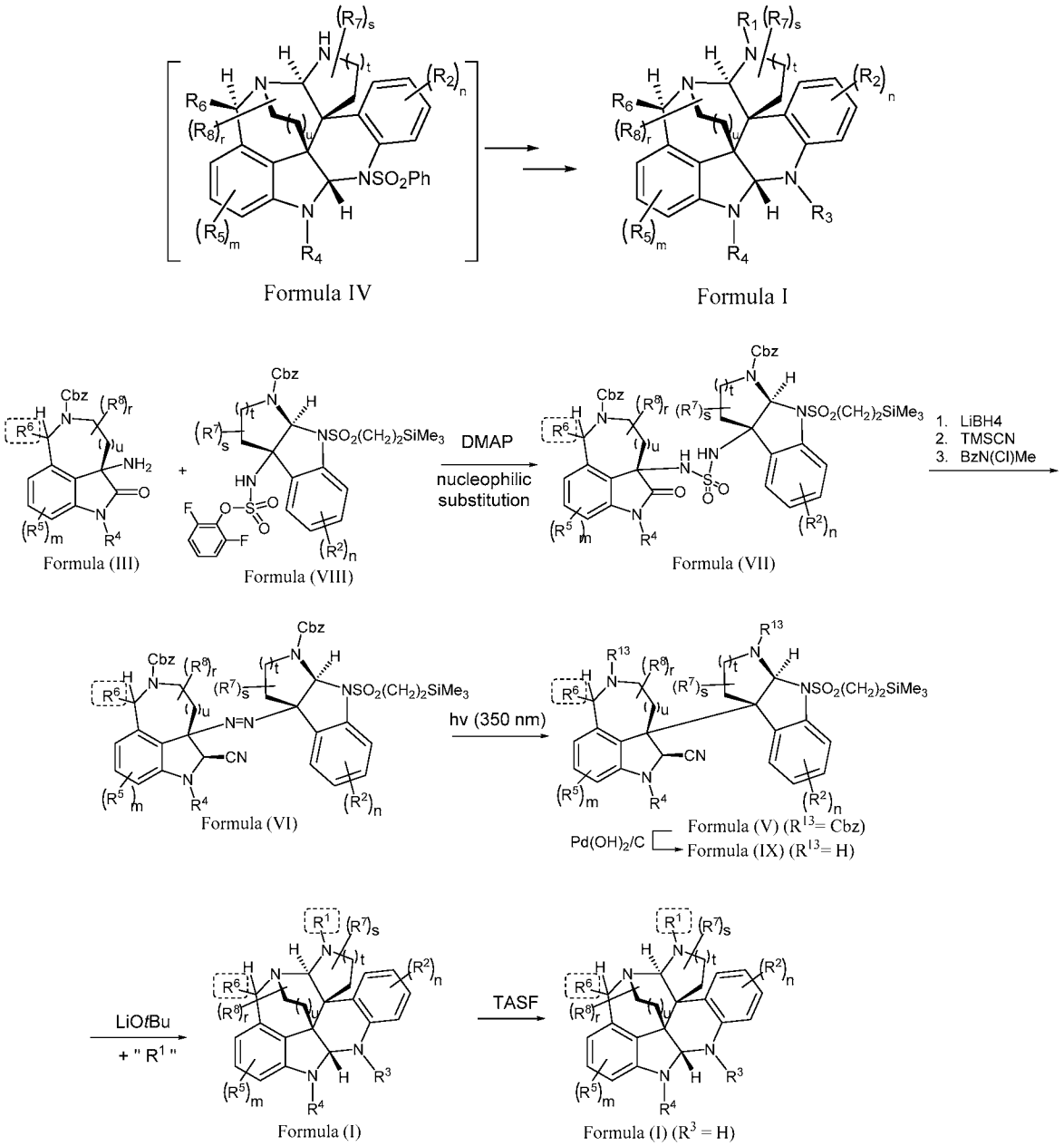
Scheme 10. Synthesis of (–)-Communesin F (**1**) via a Biogenetically Inspired Final Stage Reorganization.



[a]Reagents and conditions: (a) $Sc(OTf)_3$, F_3CCH_2OH, 23 °C; (b) *t*-BuOLi, MeOH, 50 °C; dry PPTS, Ac_2O, 23 °C; (c) Na(Hg), NaH_2PO_4, THF, MeOH, 23 °C.

[00133] Scheme 11 summarizes a representative strategy for assembling members of the communesin family and other analogs where the substituents at R^1, R^4, and R^6 are sensitive groups incompatible with the methods described above. Several modifications have been implemented. For instance, in the presence of acid-sensitive moieties, *N*-Cbz can replace *N*-Boc (Scheme 11, R^{13}), so that the conversion of a Formula (V) to Formula (IX) can be carried out with a mild reagent such as $Pd(OH)_2/C$ that is well-suited for the complex environment. Similarly, the $-SO_2Ph$ group utilized in the (–)-Communesin F total synthesis could be replaced with the SES-protecting group shown in Formula (VIII) to avoid the deleterious effects of Na/Hg in the final step towards the desired Formula (I) compounds. Accordingly, a number of previously unobtainable communesin analogs are now within reach, based on the newly developed synthesis described below.

Scheme 11. General Scheme for the Synthesis of Communesins and Analogs that Possess Sensitive Functionality at R^1 and R^6.



[00134] Appendix 1 of U.S. Provisional Application No. 62/334,826, incorporated by reference herein, provides Supporting Information including experimental procedures, spectroscopic data, crystal structure of (+)-**48** (CIF), and copies of NMR spectra. Color representations of some of the above figures, formulas, and schemes, as well as color representations of selected information from Appendix 1 are included in the attached color drawings.

[00135] In various embodiments, a highly convergent enantioselective total synthesis of (–)-communesin F (**1**) with late-stage chemistry that parallels the latest insights and hypotheses concerning the biogenesis of these alkaloids is described. This synthesis involves the union of fragments (+)-**24** and (+)-**27** to provide complex sulfamide (+)-**50** on gram-scale. This advanced intermediate is converted to alkaloid (–)-**1** in only five additional steps (Schemes 9 and 10) which include the application of our diazene–directed fragment assembly strategy to secure the congested C3a–C3a' linkage, and a guided biomimetic rearrangement to selectively provide the heptacyclic core of these alkaloids. Highlights of our synthesis include an efficient cyclotryptamine–C3a-sulfamate synthesis by either a new silver–promoted nucleophilic amination or rhodium–catalyzed C–H amination protocol, application of catalytic asymmetric halocyclization and diastereoselective oxyamination reactions in complex settings, a stereoselective sulfinimine allylation, and efficient assembly and utility of a richly functional diazene for complex fragment coupling. The successful implementation of this synthetic strategy and the versatile synthesis of the fragments, along with a final stage acylation of the communesin core provide a foundation for a unified synthetic route to access structurally related complex alkaloids and derivatives. Such derivatives can be used in therapy or as probes or tools for mechanistic investigations. A person of skill in the art will appreciate that by appropriate selection of starting materials, reagents, and reaction conditions, the schemes provided herein can be modified to provide analogs or derivatives of (–)-communesin according to Formula (I).

[00136] While various inventive embodiments have been described and illustrated herein, those of ordinary skill in the art will readily envision a variety of other means and/or structures for performing the function and/or obtaining the results and/or one or more of the advantages described herein, and each of such variations and/or modifications is deemed to be within the scope of the inventive embodiments described herein. More generally, those skilled in the art will readily appreciate that all parameters, dimensions, materials, and configurations described herein are meant to be exemplary and that the actual parameters, dimensions, materials, and/or configurations will depend upon the specific application or applications for which the inventive teachings is/are used. Those skilled in the art will recognize, or be able to ascertain using no more than routine experimentation, many equivalents to the specific inventive embodiments described herein. It is, therefore, to be understood that the foregoing embodiments are presented by way of example only and that, within the scope of the appended claims and equivalents thereto; inventive embodiments may be practiced otherwise than as specifically described and claimed. Inventive embodiments of the present disclosure are directed to each individual feature, system, article, material, kit, and/or method described herein. In addition, any combination of

two or more such features, systems, articles, materials, kits, and/or methods, if such features, systems, articles, materials, kits, and/or methods are not mutually inconsistent, is included within the inventive scope of the present disclosure.

[00137] The above-described embodiments can be implemented in any of numerous ways. Also, various inventive concepts may be embodied as one or more methods, of which an example has been provided. The acts performed as part of the method may be ordered in any suitable way. Accordingly, embodiments may be constructed in which acts are performed in an order different than illustrated, which may include performing some acts simultaneously, even though shown as sequential acts in illustrative embodiments.

[00138] In addition, those of ordinary skill in the art recognize that some functional groups can be protected/deprotected using various protecting groups before a certain reaction takes place. Suitable conditions for protecting and/or deprotecting specific functional group, and the use of protecting groups are well-known in the art.

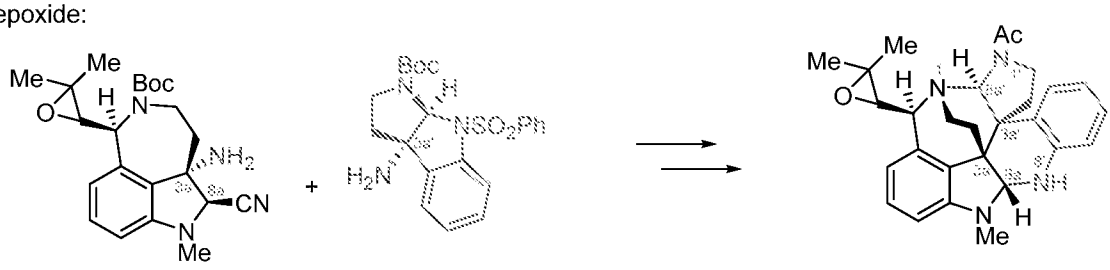
[00139] For example, various kinds of protecting groups are described in T.W. Greene and G.M. Wuts, Protecting Groups in Organic Synthesis, Second edition, Wiley, New York, 1991, and other references cited above.

[00140] All documents cited herein are herein incorporated by reference in their entirety for all purposes.

[00141] Using the methods described herein, various derivatives of communesins can be prepared from the appropriate starting materials and intermediates using the general methods described herein, as shown below in Scheme 12:

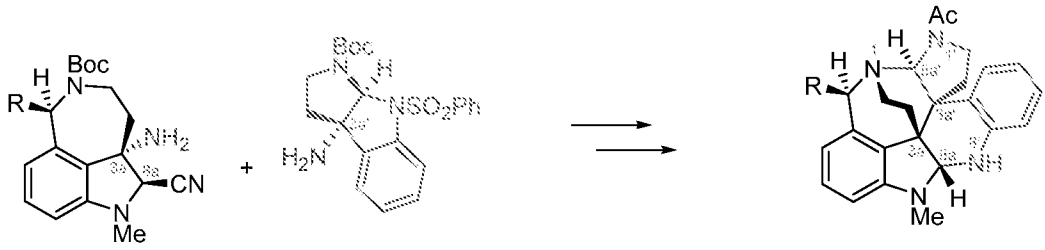
Scheme 12. Representative Classes of Communesin Derivatives.

C10-epoxide:



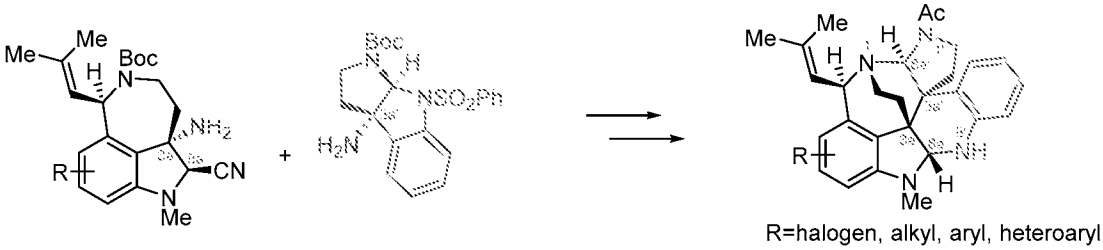
C14-expoxide
derivatives
two diastereomers

C10-derivatives:



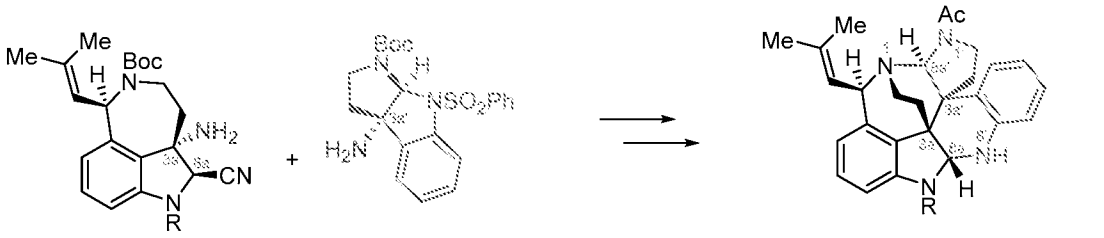
R=alkyl, aryl, heteroaryl

arene-derivatives:



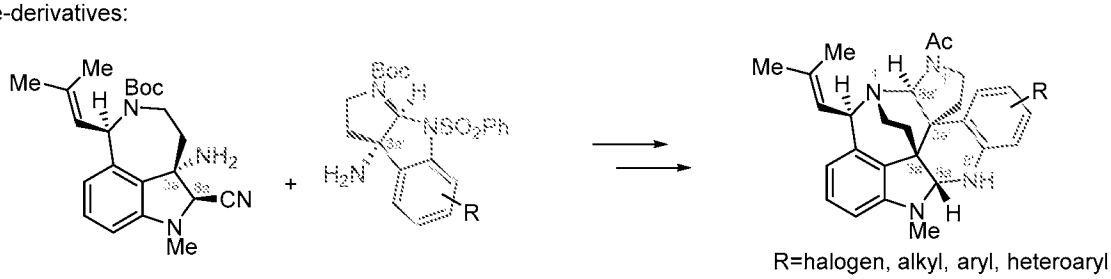
R=halogen, alkyl, aryl, heteroaryl

N8-derivatives:



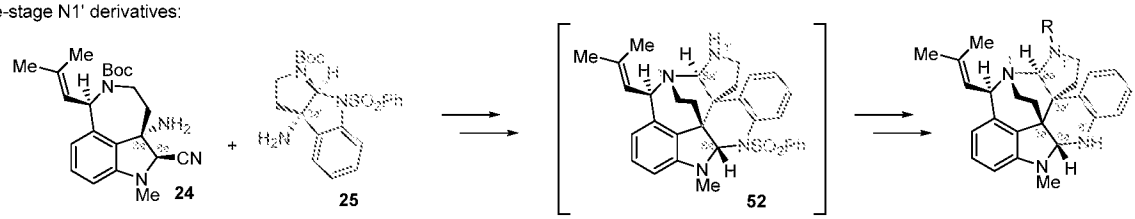
R=alkyl, aryl, heteroaryl, acyl

arene-derivatives:



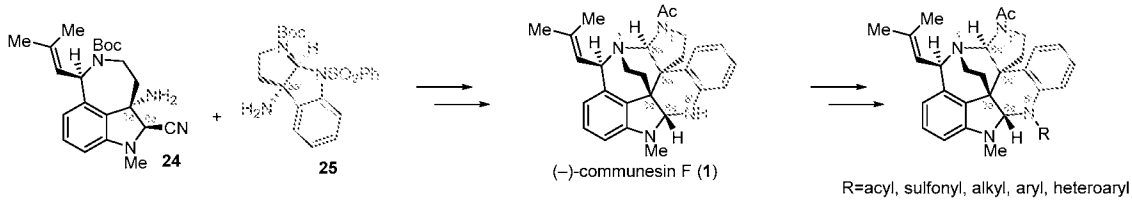
R=halogen, alkyl, aryl, heteroaryl

Late-stage N1' derivatives:

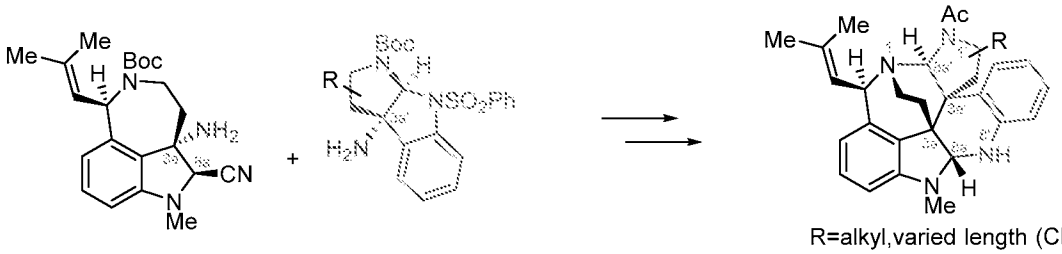


R=acyl, sulfonyl

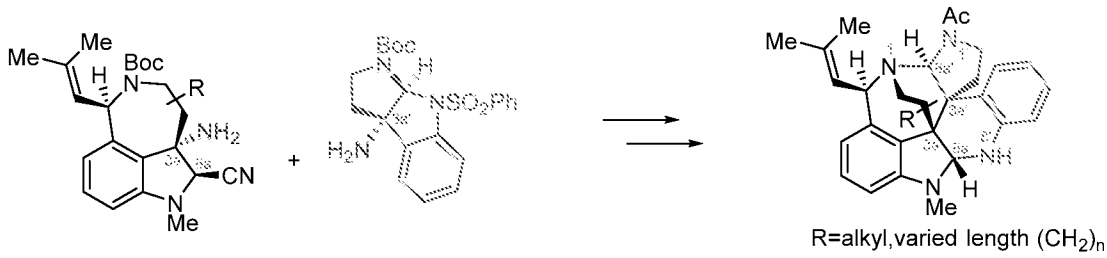
Late-stage N8' derivatives:



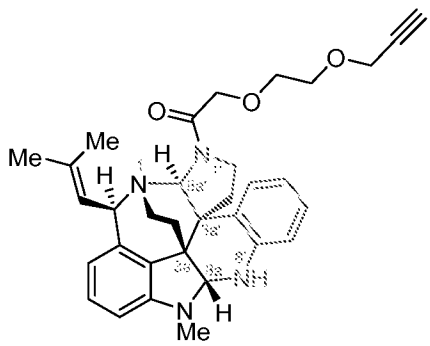
C2'/3'-derivatives:



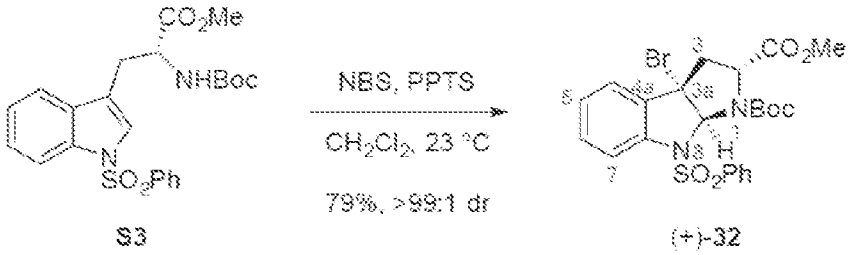
C2/3-derivatives:



[00142] The skilled artisan will also recognize that the particular variations in substitution of the communesin structure illustrated above in Scheme 12 can be combined. For example, substitution at C10 as described above can be combined with substitution at C2/3, and/or C2'/3' and/or N8, etc. These modifications can be evaluated to identify derivatives with enhanced potency for particular indications, as mechanistic probes, or for use in targeted therapy. For example, a modification as shown below can provide a "functional handle" for conjugation with an antibody (targeted delivery), for use in pull-down experiments, or as a means to attach an affinity tag or fluorophore (probe):



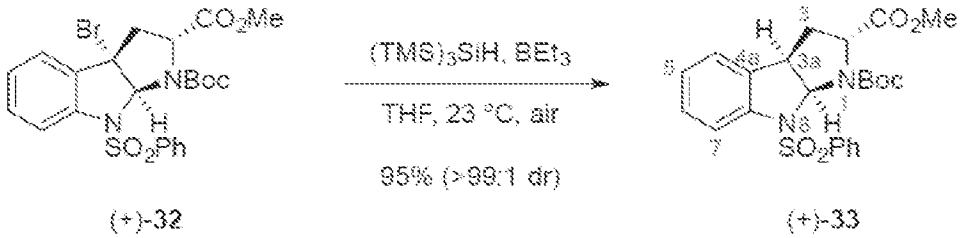
Example 1. Representative Synthesis of Formula (II) Compounds



S3 (+)-32

Bromocyclotryptophan (+)-**32**:

[00143] A sample of *N*-bromosuccinimide (4.04 g, 22.7 mmol, 1.05 equiv) was added to a solution of tryptophan derivative **S3** (9.90 g, 21.6 mmol, 1 equiv) and pyridinium *p*toluenesulfonate (5.70 g, 22.7 mmol, 1.05 equiv) in dichloromethane (216 mL) at 23 °C. After 1.5 h, the homogeneous yellow reaction mixture was washed sequentially with a saturated aqueous sodium bicarbonate solution (100 mL) followed by a saturated aqueous sodium thiosulfate solution (100 mL), and finally saturated aqueous sodium chloride solution (100 mL). The organic layer was dried over anhydrous sodium sulfate, was filtered, and was concentrated under reduced pressure. The resulting residue was purified by flash column chromatography on silica gel (eluent: 50% diethyl ether in hexanes) to afford bromocyclotryptophan (+)-**32** (11.6 g, 99.6%, 17.5:1 dr) as a white foam. The diastereomeric ratio was further enriched by recrystallization from 27% ethyl acetate in hexanes to yield bromocyclotryptophan (+)-**32** (9.13 g over two batches, 78.7%, >99:1 dr) as colorless plates.

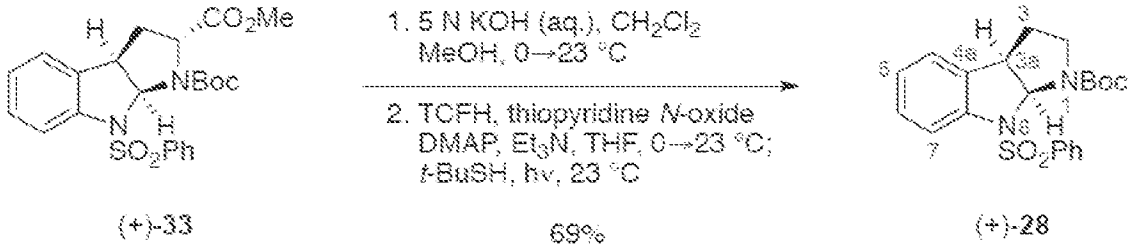


(+)-**32** (+)-**33**

Cyclotryptophan (+)-**33**:

[00144] Triethylborane (1.0 M in THF, 1.7 mL, 1.7 mmol, 0.10 equiv) was added via syringe to a solution of bromocyclotryptophan (+)-**32** (9.01g, 16.7 mmol, 1 equiv) and tris(trimethylsilyl)silane (15.5 mL, 50.1 mmol, 3.00 equiv) in tetrahydrofuran (129 mL) at 23 °C under an air atmosphere. After 10 min, the homogeneous colorless solution was diluted with a saturated aqueous sodium bicarbonate solution (130 mL). After vigorous stirring for 10 min, the heterogeneous biphasic mixture was diluted with deionized water (100 mL) then extracted with dichloromethane (3 × 200 mL). The combined organic extracts were dried over anhydrous sodium sulfate, were filtered, and were concentrated under reduced pressure to yield a colorless semi-solid suspended in a colorless oil. The colorless oil was decanted and the remaining residue was purified via flash chromatography on silica gel (eluent: 25% → 32% ethyl acetate in

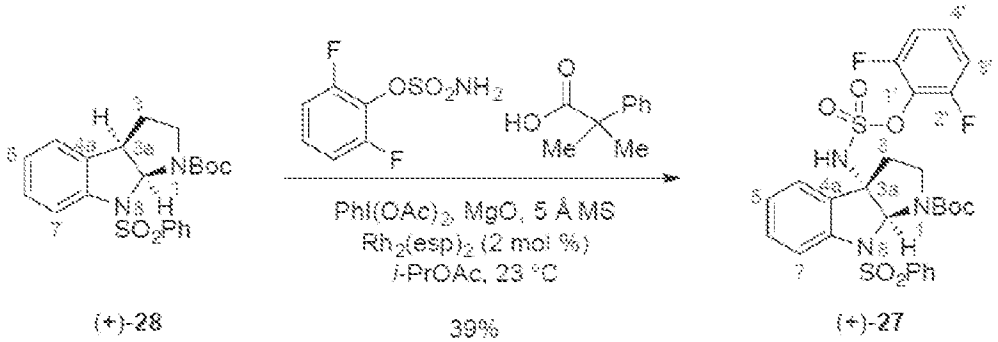
hexanes) to afford cyclotryptophan (+)-**33** (7.27 g, 94.9%, >99:1 dr) as a white foam.



Cyclotryptamine (+)-**28**:

[00145] An aqueous sodium hydroxide solution (5 N, 79.0 mL, 395 mmol, 25.0 equiv) was added in portions over 5 min to a solution of cyclotryptophan (+)-**33** (7.25 g, 15.7 mmol, 1 equiv) in methanol (240 mL) and dichloromethane (31 mL) cooled to 0 °C in an ice bath under an air atmosphere. After 5 min, the ice bath was removed and the milky white solution was allowed to stir at 23 °C. After 7 h, the reaction mixture was cooled to 0 °C in an ice bath and acidified to pH~ 3 by the portionwise addition of an aqueous hydrochloric acid solution (12 N, 34 mL) over 10 min. The resulting white suspension was allowed to warm to 23 °C and was then concentrated under reduced pressure to remove methanol. The white suspension was then diluted with deionized water (100 mL) and extracted with dichloromethane (3 × 200 mL). The combined organic extracts were washed with a saturated aqueous sodium chloride solution (100 mL), were dried over anhydrous sodium sulfate, were filtered, and were concentrated under reduced pressure to afford the crude carboxylic acid (8.0 g, >99%) as a white foam, which was used directly in the next step after azeotropic drying by concentration from toluene (HPLC grade, 3 × 100 mL). Samples of 2-mercaptopyridine *N*-oxide (3.20 g, 25.2 mmol, 1.60 equiv), 4-(dimethylamino)pyridine (192 mg, 1.57 mmol, 0.100 equiv), and *N,N,N',N'*-tetramethylchloroformamidinium hexafluorophosphate (TCFH, 6.62 g, 23.6 mmol, 1.50 equiv) were added sequentially to a solution of the crude carboxylic acid in tetrahydrofuran (157 mL) cooled to 0 °C in an ice bath. The reaction flask was subsequently removed from the ice bath, covered in aluminum foil, and charged with triethylamine (8.80 mL, 63.0 mmol, 4.00 equiv) in a slow stream over 30 s while the reaction mixture was still cold. After 2.75 h, *tert*-butyl mercaptan (8.90 mL, 78.7 mmol, 5.00 equiv) was added via syringe. The aluminum foil was then removed from the flask and the resulting green suspension was irradiated with a flood lamp (500 W). To maintain an internal temperature of 23 °C, the flask was immersed in a 20 °C water bath. After 2 h, the lamp was shut off and a saturated aqueous sodium bicarbonate–water solution (1:1, 400 mL) was added. The aqueous layer was extracted with dichloromethane (3 × 200 mL). The combined organic extracts were washed with a saturated aqueous sodium chloride solution (150

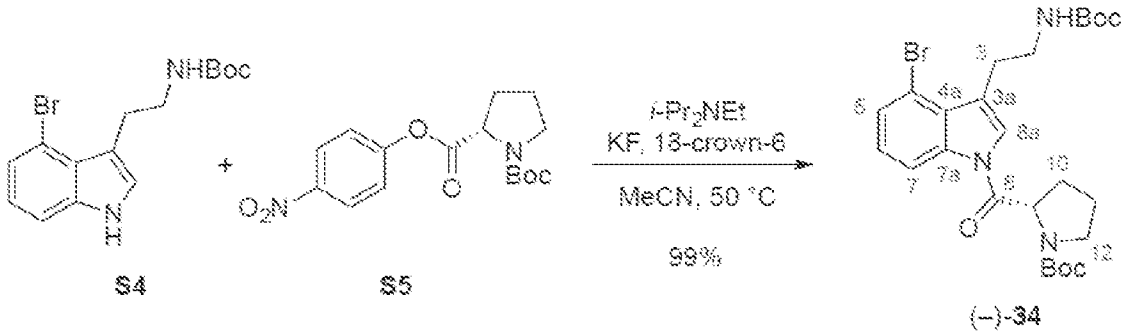
mL), were dried over anhydrous sodium sulfate, were filtered, and were concentrated under reduced pressure. The resulting residue was purified by flash column chromatography on silica gel (eluent: 20 → 25% acetone in hexanes) to afford cyclotryptamine (+)-**28** (4.35 g, 69.0% overall from (+)-**33**) as a white foam.



Sulfamate ester (+)-**27**:

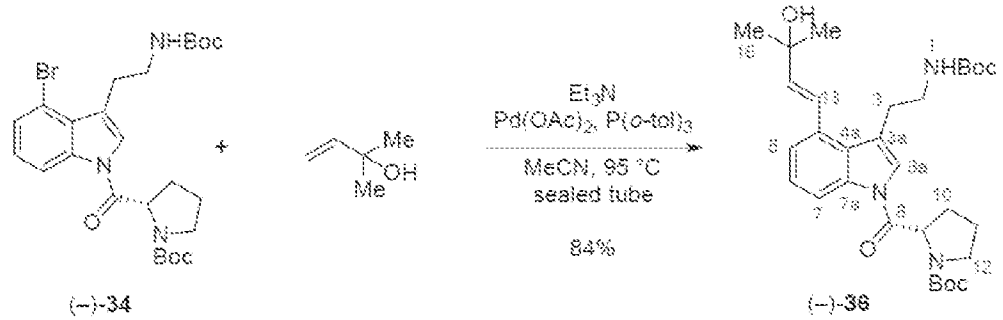
[00146] A round bottom flask equipped with a stir bar was charged with crushed 5Å molecular sieves (1.06 g, 200 mg/mmol of **28**), and magnesium oxide (853 mg, 21.2 mmol, 4.00 equiv). The flask and its contents were flame-dried under vacuum for 7 min. The reaction vessel was allowed to cool to 23 °C and was then backfilled with argon. Bis[rhodium(α,α,α',α'-tetramethyl-1,3-benzenedipropionic acid)] (80.2 mg, 106 μmol, 0.0200 equiv), cyclotryptamine (+)-**28** (2.13 g, 5.29 mmol, 1 equiv), 2,6-difluorophenyl sulfamate5 (1.44 g, 6.88 mmol, 1.30 equiv), and 2-methyl-2-phenylpropionic acid (434 mg, 2.65 mmol, 0.500 equiv) were then added sequentially. The flask was evacuated and backfilled with argon (three cycles) and was then charged with isopropyl acetate (7.0 mL). The resulting green suspension was stirred vigorously for 5 min then (diacetoxyiodo) benzene (3.41 g, 10.6 mmol, and 2.00 equiv) was added in a single portion. The flask was sealed and the suspension was allowed to stir vigorously at 23 °C under a static atmosphere of argon. After 26 h, the reaction mixture was filtered through a pad of Celite and the filter cake was rinsed with ethyl acetate (50 mL). The filtrate was concentrated under reduced pressure and the resulting residue was purified by flash column chromatography on silica gel (eluent: 20 → 30% acetone in hexanes) to afford a mixture of the desired sulfamate ester (+)-**27** along with a minor amount of the regioisomeric C2 amination product (5.4:1). The mixture was further purified by recrystallization from dichloromethane, hexanes, and diethyl ether (1:1:1, 4.5 mL) at 5 °C to afford exclusively the sulfamate ester (+)-**27** (1.26 g, 39.2%) as an off-white solid.

Example 2: Representative Synthesis of Formula (III) Compounds



Amide (–)-**34**:

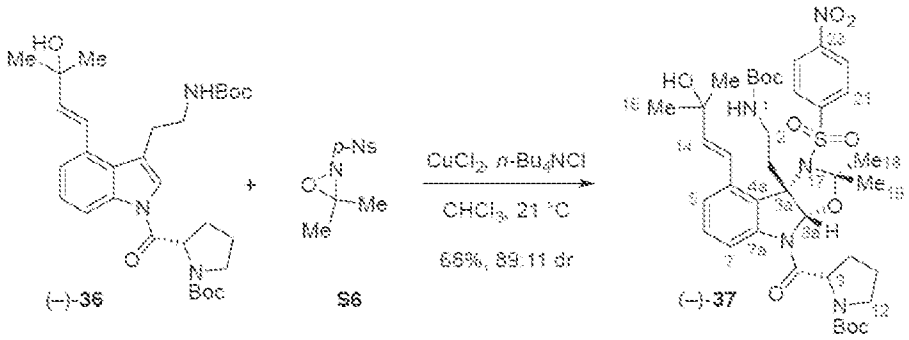
[00147] A 100 mL Schlenk flask containing a magnetic stir-bar was charged with 18-crown-6 (5.50 g, 20.8 mmol, 2.00 equiv), potassium fluoride (2.44 g, 41.6 mmol, 4.00 equiv), bromotryptamine **S4** (3.53 g, 10.4 mmol, 1 equiv), and L-proline derivative **S5** (6.12 g, 18.2 mmol, 1.75 equiv) sequentially.7 The reaction flask and its contents were placed under vacuum and backfilled with argon (three cycles). Acetonitrile (42 mL) and *N,N*-diisopropylethylamine (6.40 mL, 46.8 mmol, 4.50 equiv) were then added. The resulting bright yellow heterogeneous mixture was sonicated for 1 h and then the flask was immersed in a pre-heated oil bath at 50 °C and stirred vigorously for 16 h. The reaction mixture was concentrated under reduced pressure. The residue was dissolved in ethyl acetate (100 mL) and was washed sequentially with deionized water (50 mL), a saturated aqueous potassium carbonate–water solution (1:1, 2 × 50 mL), deionized water (50 mL), and a saturated aqueous sodium chloride solution (2 × 50 mL). The organic phase was dried over anhydrous sodium sulfate, was filtered, and was concentrated under reduced pressure. The resulting light brown oil was purified by flash column chromatography on silica gel (eluent: 10% → 40% ethyl acetate in hexanes) to afford amide (–)-**34** (5.50 g, 98.6%) as a white foam.



Allylic alcohol (–)-**36**:

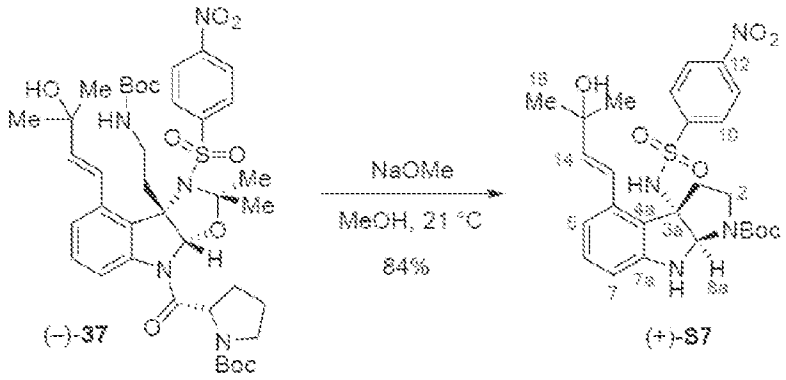
[00148] Acetonitrile (10.8 mL), triethylamine (2.00 mL, 14.5 mmol, 1.50 equiv), and 1,1-dimethylallyl alcohol (4.65 mL, 43.6 mmol, 4.50 equiv) were sequentially added to a 100 mL

pressure tube containing palladium(II) acetate (174 mg, 0.78 mmol, 0.0800 equiv), tri(*o*-tolyl) phosphine (590 mg, 1.94 mmol, 0.200 equiv), and amide (–)-**34** (5.20 g, 9.69 mmol, 1 equiv). The reaction tube was sealed under an argon atmosphere and immersed in a pre-heated oil bath at 95 °C. After 3.5 h, the reaction mixture was cooled to 23 °C and was filtered through a pad of silica gel. The filter cake was washed with ethyl acetate (100 mL) and the filtrate was concentrated under reduced pressure. The thick orange oil was purified by flash column chromatography on silica gel (eluent: 10% →75% acetone in hexanes). The resulting yellow sticky foam was purified by flash column chromatography on silica gel (eluent: 10% → 40% ethyl acetate in hexanes) to afford allylic alcohol (–)-**36** (4.40 g, 83.8%) as a white foam.



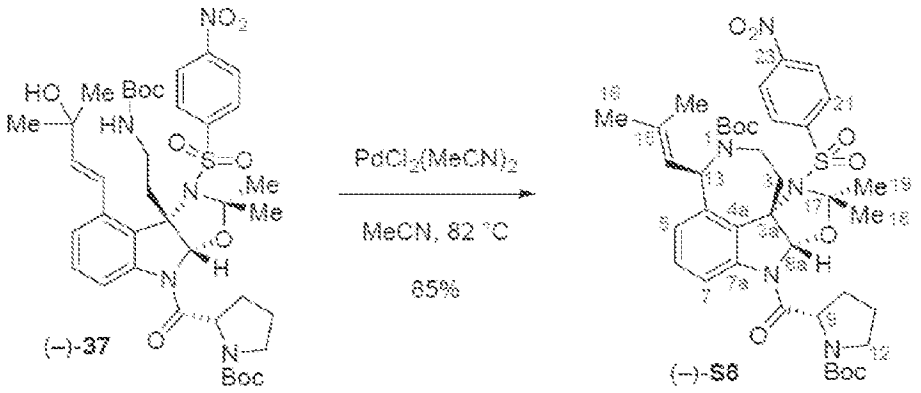
Oxazoline (–)-**37**:

[00149] Copper(II) chloride (1.03 g, 7.62 mmol, 1.00 equiv) and tetra-*n*-butylammonium chloride8 (4.13 g, 7.62 mmol, 1.00 equiv) were added to a 100 mL Schlenk flask. Chloroform (38 mL) was added and the resulting dark red mixture was stirred vigorously for 20 min, at which point allylic alcohol (–)-**36** (4.13 g, 7.62 mmol, 1 equiv) and oxaziridine **S69** (2.56 g, 9.91 mmol, 1.30 equiv) were added. After stirring at 21 °C for 1.5 h, the reaction mixture was filtered through a pad of silica gel, and the filter cake was washed with an ethyl acetate–hexanes solution (1:1, 800 mL). The yellow filtrate was concentrated under reduced pressure and the residue was purified by flash column chromatography on silica gel (eluent: 10% → 40% ethyl acetate in hexanes). Further purification by chromatography on silica gel (eluent: 10% → 30% acetone in hexanes) afforded oxazoline (–)-**37** (4.16 g, 68.1%) as a pale yellow foam as an inseparable mixture of diastereomers (89:11 dr). The diastereomeric ratio was determined after derivatization of oxazoline (–)-**37**.



Aminocyclotryptamine (+)-S7:

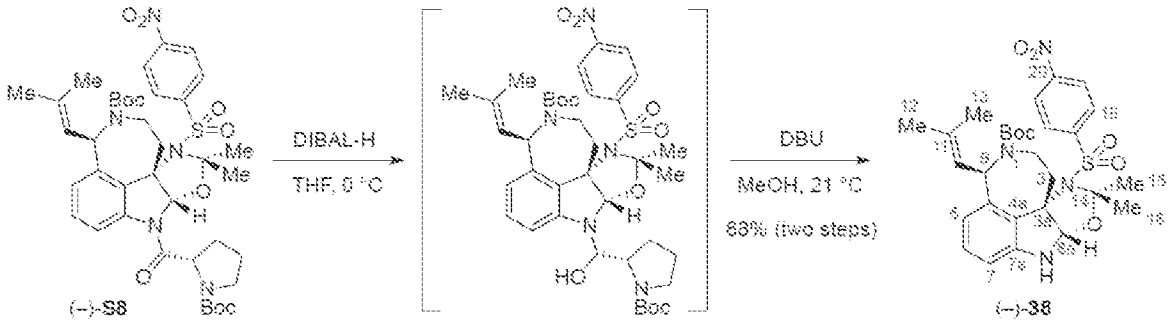
[00150] A solution of sodium methoxide (142 mg, 2.50 mmol, 50.0 equiv) in methanol (1.0 mL) was added to a solution of oxazoline (–)-**37** (40.0 mg, 50.0 μmol, 1 equiv) in methanol (0.5 mL). After stirring at 21 °C for 24 h, the light yellow solution was diluted with a mixture of saturated aqueous ammonium chloride–water (1:1, 10 mL) and was extracted with dichloromethane (5 × 5 mL). The combined extracts were dried over anhydrous sodium sulfate, were filtered, and were concentrated under reduced pressure. The resulting yellow film was purified by flash column chromatography on silica gel (eluent: 10% → 40% ethyl acetate in hexanes) to afford aminocyclotryptamine (+)-S7 (4.40 g, 83.8%, 89:11 er) as a yellow solid. The enantiomeric ratio was determined by chiral HPLC analysis (Chiralpak IA, 80% *i*PrOH / 20% hexanes, 1.0 mL/min, 254 nm, t_R (major) = 7.8 min, t_R (minor) = 6.5 min).



Azepine (–)-S8:

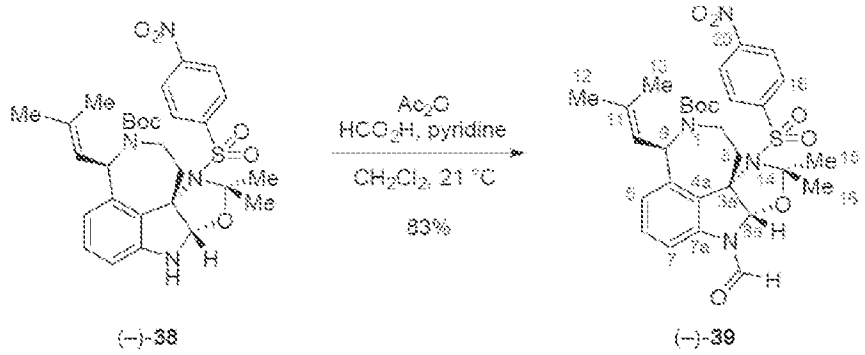
[00151] Acetonitrile (70 mL) was added to a pressure tube containing bis(acetonitrile)-dichloropalladium(II) (190 mg, 720 μmol, 0.15 equiv) and oxazoline (–)-**37** (89:11 dr, 3.85 g, 4.81 mmol, 1 equiv). The tube was sealed under an argon atmosphere and was immersed in a pre-heated oil bath at 82 °C. After 4 h, the orange solution was cooled to 21 °C and the solvent was then removed under reduced pressure. The orange residue was purified by flash column

chromatography on silica gel (eluent: 10% → 20% acetone in hexanes) to afford azepine (–)-**S8** (3.19 g, 84.8%) as a white powder.



Indoline (–)-**38:**

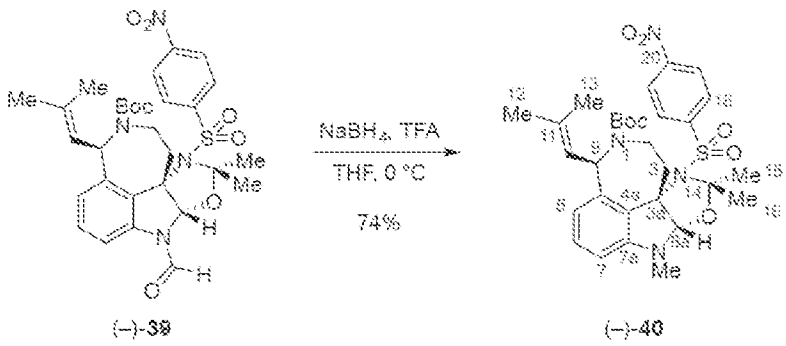
[00152] A solution of azepine (–)-**S8** (3.10 g, 3.96 mmol, 1 equiv) in tetrahydrofuran (59 mL) was cooled to −20 °C and diisobutylaluminum hydride (1.0 M in hexanes, 11.9 mL, 11.0 mmol, 3.00 equiv) was added dropwise over 10 min. After 2 min, the reaction mixture was warmed to 0 °C and the orange solution was allowed to stir at this temperature. After 3 h, excess reducing agent was quenched cautiously by the dropwise addition of deionized water (11.9 mL). After gas evolution had subsided, an aqueous sodium hydroxide solution (1 N, 60 mL) was added. The resulting mixture was stirred vigorously for 15 min and was then extracted with ethyl acetate (3 × 120 mL). The combined organic extracts were dried over anhydrous sodium sulfate, were filtered through a pad of Celite, and were concentrated under reduced pressure. The residual ethyl acetate in the residue was removed by concentration from hexanes (3 × 20 mL) under reduced pressure to furnish crude hemiaminal intermediate as a yellow solid, containing a minor amount of the desired indoline (–)-**38** based on TLC analysis. The crude mixture was dissolved in methanol (32 mL) at 21 °C and 1,8- diazabicycloundec-7-ene (890 µL, 5.95 mmol, 1.50 equiv) was added via syringe. After stirring for 2.5 h, the solvent was removed under reduced pressure and the resulting orange oil was filtered through a pad of silica gel, washing the filter cake with ethyl acetate–hexanes solution (1:1, 250 mL). The filtrate was concentrated and the resulting orange oil was purified by flash column chromatography on silica gel (eluent: 10% → 20% ethyl acetate in hexanes) to afford indoline (–)-**38** (2.04 g, 87.9%) as a bright yellow solid.



(–)-38 (–)-39

Formamide (–)-**39**:

[00153] A mixture of acetic anhydride (3.20 mL, 34.0 mmol, 10.0 equiv) and formic acid (1.30 mL, 34.0 mmol, 10.0 equiv) was added to a solution of indoline (–)-**38** (1.98 g, 3.38 mmol, 1 equiv) and pyridine (274 μL, 3.39 mmol, 1.00 equiv) in dichloromethane (13.5 mL) at 0 °C.10 The reaction mixture was warmed to 21 °C and stirred vigorously. After 2 h, a saturated aqueous sodium bicarbonate solution (80 mL) was slowly introduced and the resulting mixture was stirred vigorously for 1 h, at which time gas evolution had ceased. The layers were separated and the aqueous layer was extracted with dichloromethane (3 × 40 mL). The combined organic extracts were dried over anhydrous sodium sulfate, were filtered, and were concentrated under reduced pressure to give a light yellow solid. Purification by flash column chromatography on silica gel (eluent: 10% → 40% ethyl acetate in hexanes) afforded formamide (–)-**39** as a light yellow solid. This solid was suspended in hexanes (60 mL) and was filtered to provide formamide (–)-**39** (1.72 g, 83.1%) as a white solid.

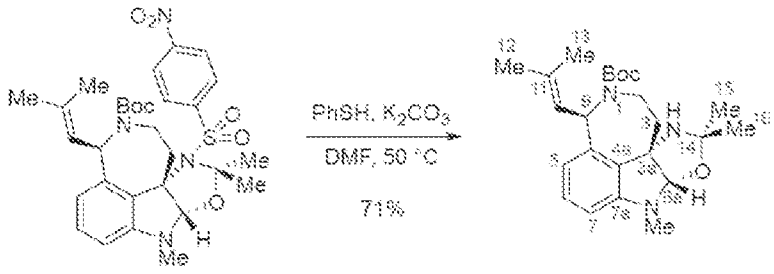


(–)-39 (–)-40

N-Methyl indoline (–)-**40**:

[00154] A sample of sodium borohydride (643 mg, 16.6 mmol, 6.00 equiv) was added to a solution of formamide (–)-**39** (1.70 g, 2.77 mmol, 1 equiv) in tetrahydrofuran (55 mL). The resulting suspension was cooled to 0 °C and trifluoroacetic acid (1.27 g, 16.6 mmol, 6.00 equiv) was then added. After stirring at this temperature for 1.5 h, excess sodium borohydride was

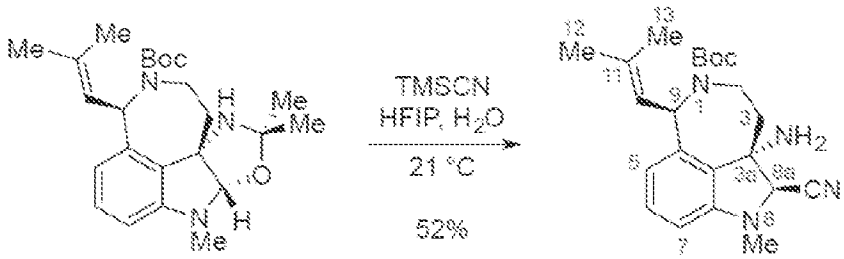
quenched by slow addition of a saturated aqueous sodium bicarbonate solution (55 mL). The resulting white suspension was diluted with deionized water (55 mL) and was extracted with ethyl acetate (3 × 120 mL). The combined organic extracts were dried over anhydrous sodium sulfate, were filtered, and were concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (eluent: 20% ethyl acetate in hexanes) to afford *N*-methyl indoline (–)-**40** (1.22 g, 73.5%) as a yellow solid.



(–)-40 (–)-41

Hemiaminal (–)-**41**:

[00155] Thiophenol (1.0 mL, 10 mmol, 10 equiv) was added to a mixture of *N*-methyl indoline (–)-**40** (0.620 g, 1.00 mmol, 1 equiv) and potassium carbonate (1.43 g, 10.4 mmol, 10.0 equiv) in dimethylformamide (10.4 mL) and the resulting brown suspension was heated to 50 °C. After 2 h, the reaction mixture was cooled to 21 °C, was diluted with deionized water (100 mL), and was extracted with diethyl ether (4 × 100 mL). The combined organic extracts were dried over anhydrous sodium sulfate, were filtered, and were concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (eluent: 10% → 20% ethyl acetate in hexanes). A second chromatographic purification on silica gel (eluent: 0% → 10% ethyl acetate in dichloromethane) followed by azeotropic drying of the sticky foam with toluene furnished hemiaminal (–)-**41** (304 mg, 70.9%) as a white solid.

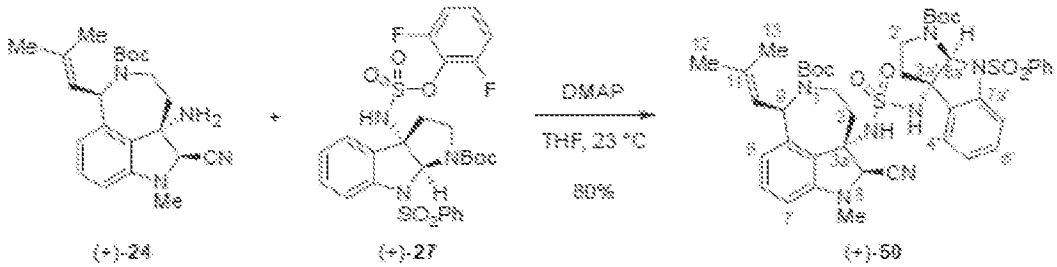


(–)-41 (+)-24

Tricyclic amine (+)-**24**:

[00156] A pressure tube containing hemiaminal (–)-**41** (62 mg, 0.15 mmol, 1 equiv) was cooled to 0 °C and was charged sequentially with trimethylsilyl cyanide (58 μL, 0.45 mmol, 3.0 equiv), anhydrous hexafluoroisopropanol (58 μL, 0.54 mmol, 3.6 equiv), and water (8.1 μL, 0.45 mmol, 3.0 equiv). The mixture was warmed to 21 °C and the tube was quickly sealed under an argon atmosphere. After 10 days, an aqueous sodium hydroxide solution (1 N, 1.5 mL) was introduced and the resulting mixture was extracted with dichloromethane (3 x 2 mL). The combined organic extracts were dried over anhydrous sodium sulfate, were filtered, and were concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (eluent: 10% → 30% ethyl acetate in hexanes) to afford tricyclic amine (+)-**24** (30.0 mg, 52.3%, R*f*: 0.23; 50% ethyl acetate in hexanes) as a white foam and the C8a-epimer (15.0 mg, 26.1%, R*f*: 0.85; 50% ethyl acetate in hexanes) as a white foam.

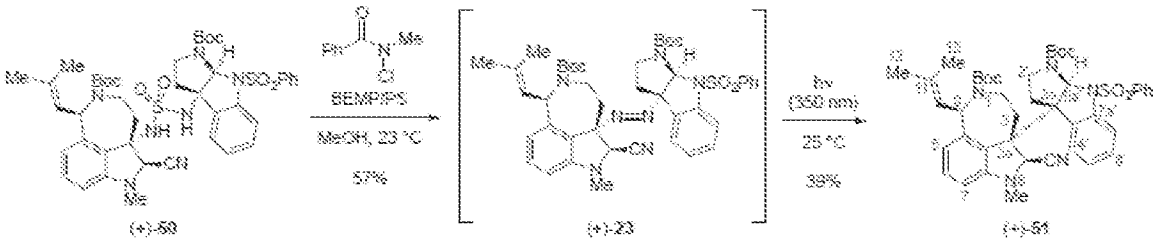
Example 3: Representative synthesis of Formula (V) compounds.



(+)-24 (+)-27 (+)-50

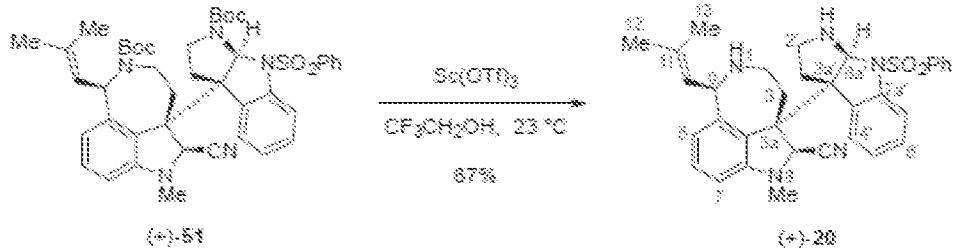
Sulfamide (+)-**50**:

[00157] A sample of 4-(dimethylamino)pyridine (518 mg, 4.24 mmol, 2.50 equiv) was added to a solution of tricyclic amine (+)-**24** (662 mg, 1.70 mmol, 1 equiv) and sulfamate ester (+)-**27** (1.21 g, 1.98 mmol, 1.17 equiv) in tetrahydrofuran (8.5 mL) at 23 °C. After 20 h, deionized water (50 mL) was added and the mixture was extracted with dichloromethane (3 × 50 mL). The combined organic extracts were washed with a saturated aqueous sodium chloride solution (35 mL), were dried over anhydrous sodium sulfate, were filtered, and were concentrated under reduced pressure. The resulting residue was purified by flash column chromatography on silica gel (eluent: 20% →30% ethyl acetate in hexanes) to afford sulfamide (+)-**50** (1.17 g, 80.0%) as an off-white foam.



Heterodimer (+)-**51:**

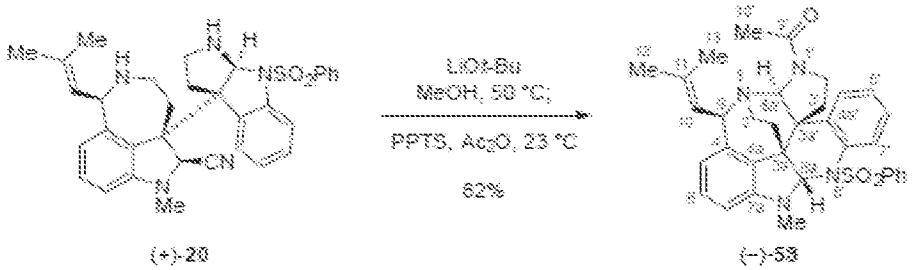
[00158] To a solution of sulfamide (+)-**50** (300 mg, 349 μmol, 1 equiv) in methanol (34.9 mL) in the dark was added *N*-chloro-*N*-methylbenzamide16 (**S11**, 355 mg, 2.09 mmol, 6.00 equiv) followed immediately by resin-bound BEMP (1.90 g, ~2.2 mmol/g on 200-400 mesh polystyrene resin, 4.19 mmol, 12.0 equiv) in a single portion. After 18 min, the suspension was filtered through a pad of Celite, and the filter cake was washed sequentially with dichloromethane (60 mL) and ethyl acetate (60 mL). The light yellow filtrate was concentrated under reduced pressure and the resulting residue was purified by flash column chromatography on silica gel in low light (eluent: 15%→20% ethyl acetate in hexanes) to afford unsymmetrical diazene (+)-**23** (157 mg, 56.6%) as a light yellow oil, which slowly solidified under reduced pressure.17 Unsymmetrical diazene (+)-**23** was used directly in the next step without further purification. A solution of unsymmetrical diazene (+)-**23** (155 mg, 195 μmol, 1 equiv) in dichloromethane (15 mL) was concentrated under reduced pressure in a 200 mL round bottom flask to provide a thin film of diazene (+)-**23** coating the flask. The flask was evacuated and backfilled with argon (three cycles) and was then irradiated in a Rayonet photoreactor equipped with 16 radially distributed (r = 12.7 cm) 25 W lamps (λ = 350 nm) at 25 °C. After irradiating for 3 h, the lamps were shut off and the resulting residue was purified by flash column chromatography on silica gel (eluent: 20% ethyl acetate in hexanes) to afford an inseparable mixture (~1:1) of heterodimer (+)-**51** and cyclotryptamine **28** according to ^{1}H NMR analysis (91.4 mg, 38.7% corrected yield of **51**) as an off-white foam. This mixture was used directly in the next step without further purification.



Heterodimeric diamine (+)-**20**:

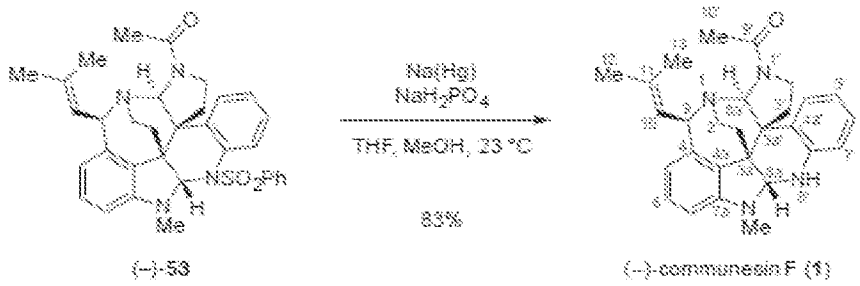
[00159] A sample of scandium(III) trifluoromethanesulfonate (223 mg, 452 μmol, 6.00 equiv) was added to an inseparable mixture of heterodimer (+)-**51** (57.8 mg, 75.4 μmol, 1 equiv) and cyclotryptamine **28** (31.2 mg, 77.8 μmol, 1.03 equiv) dissolved in 2,2,2-trifluoroethanol (7.50 mL) at 23 °C. After 25 min, a saturated aqueous sodium bicarbonate solution (15 mL) was added and the mixture was extracted with dichloromethane (3 × 15 mL). The combined organic extracts were washed with a saturated aqueous sodium chloride solution (15 mL), were dried over anhydrous sodium sulfate, were filtered, and were concentrated under reduced pressure. The resulting residue was purified by flash column chromatography on silica gel (eluent: 33% acetone, 1% methanol in dichloromethane) to afford heterodimeric diamine (+)-**20** (28.4 mg, 66.6%) as a light tan foam.

Example 4. Representative Synthesis of Formula (I) compounds.



N8′-Benzenesulfonyl Communesin F (–)-**53:**

[00160] A solution of lithium *tert*-butoxide (0.100 M in MeOH, 1.13 mL, 113 μmol, 10.0 equiv) was added to a solution of heterodimer (+)-**20** (6.30 mg, 11.1 μmol, 1 equiv) in methanol (1.13 mL). The vessel was sealed then immersed in a preheated 50 °C oil bath and was allowed to stir under a static atmosphere of argon. After 4 h, the reaction mixture was cooled to 23 °C, after which pyridinium *p*-toluenesulfonate (22.4 mg, 89.1 μmol, 8.00 equiv) and acetic anhydride (9.5 μL, 100 μmol, 9.00 equiv) were added sequentially. After 24 min, a saturated aqueous sodium bicarbonate solution (3 mL) was added and the resulting heterogeneous mixture was diluted with deionized water (5 mL) then extracted with dichloromethane (3 × 10 mL). The combined organic extracts were washed with a saturated aqueous sodium chloride solution (10 mL), were dried over anhydrous sodium sulfate, were filtered, and were concentrated under reduced pressure. The residue was purified via flash column chromatography (eluent: 25% → 30% acetone in hexanes) to afford *N8′*-benzenesulfonyl communesin F (–)-**53** (5.3 mg, 82%) as a white solid.

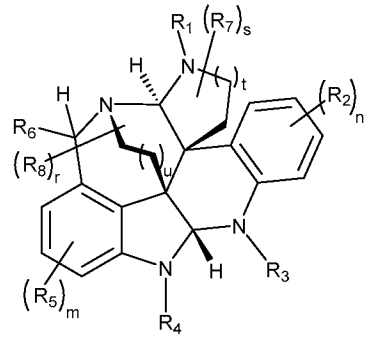


(–)-Communesin F (**1**):

[00161] A sample of sodium amalgam18 (5%-Na, 160 mg, 348 μmol, 20.0 equiv) was added to a suspension of sodium phosphate monobasic monohydrate (52.6 mg, 383 μmol, 22.0 equiv) and *N*8′-benzenesulfonyl communesin F (–)-**53** (10.1 mg, 17.4 μmol, 1 equiv) in tetrahydrofuran (250 μL) and methanol (750 μL) at 23 °C. After 20 min, another portion of sodium phosphate monobasic monohydrate (52.6 mg, 383 μmol, 22.0 equiv) and sodium amalgam (5%-Na, 160 mg, 348 μmol, 20.0 equiv) were added sequentially. After an additional 20 min, another portion of sodium phosphate monobasic monohydrate (52.6 mg, 383 μmol, 22.0 equiv) and sodium amalgam (5%-Na, 160 mg, 348 μmol, 20.0 equiv) were added sequentially. After an additional 20 min, a final portion of sodium phosphate monobasic monohydrate (52.6 mg, 383 μmol, 22.0 equiv) and sodium amalgam (5%-Na, 160 mg, 348 μmol, 20.0 equiv) were added sequentially. After 30 min, an aqueous solution of 5% sodium bicarbonate (5 mL) was added and the resulting mixture was extracted with dichloromethane (3 × 10 mL). The combined organic extracts were washed with a saturated aqueous sodium chloride solution (5 mL), were dried over anhydrous sodium sulfate, were filtered, and were concentrated under reduced pressure. The resulting residue was purified by flash column chromatography on silica gel (eluent: 25% → 33% acetone in hexanes) to afford (–)-communesin F (**1**) (6.40 mg, 83.1%) as a white solid.

What is claimed is:

1. A compound of Formula (I):



Formula (I)

or a pharmaceutically acceptable salt, tautomer or stereoisomer thereof, wherein:

R^1, R^3, and R^4 are each independently selected from H, C_1-C_{12} alkyl, C_2-C_{12} alkenyl, C_2-C_{12} alkynyl, -C(=O)R^9, -C(=O)NR^9R^{10}, -S(=O)$_u$$R^{12}$, aryl, heteroaryl, carbocyclyl, or heterocyclyl, wherein R^3 and R^4 taken together with the carbon atoms to which they are attached form an aryl, heteroaryl, carbocyclic, or heterocyclic ring;

R^2 and R^5 are each independently selected from F, Cl, Br, I, -OH, -OR^9, -OC(=O)R^9, -S(=O)$_u$$R^{12}$, -$NR^9R^{10}$, C_1-C_{12} alkyl, C_2-C_{12} alkenyl, C_2-C_{12} alkynyl, aryl, heteroaryl, carbocyclyl, or heterocyclyl;

R^6 is independently H, -OH, -OR^9, -OC(=O)R^9, -S(=O)$_u$$R^{12}$, -$NR^9R^{10}$, C_1-C_{12} alkyl, C_1-C_{12} alkyl, C_2-C_{12} alkenyl, C_2-C_{12} alkynyl aryl, heteroaryl, carbocyclyl, or heterocyclyl;

R^7 and R^8 are each independently selected from H, C_1-C_{12} alkyl; C_2-C_{12} alkenyl, C_2-C_{12} alkynyl, -C(=O)R^9, -C(=O)NR^9R^{10}, -S(=O)$_u$$R^{12}$, -OH, -O$R^9$, -OC(=O)$R^9$, -$NR^9R^{10}$, aryl, heteroaryl, carbocyclyl, or heterocyclyl, wherein two R^7 or two R^8 groups taken together with the carbon atoms to which they are attached form an aryl, heteroaryl, carbocyclic, or heterocyclic ring;

R^9 and R^{10} are each independently selected from H, C_1-C_{12} alkyl, C_2-C_{12} alkenyl, C_2-C_{12} alkynyl, aryl, heteroaryl, carbocyclyl, or heterocyclyl, wherein R^9 and R^{10} taken together with the carbon atoms to which they are attached form an aryl, heteroaryl, carbocyclic, or heterocyclic ring;

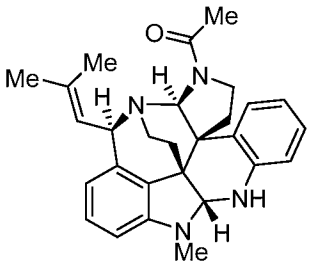
R^{12} is C_1-C_{12} alkyl, C_2-C_{12} alkenyl, C_2-C_{12} alkynyl, aryl, heteroaryl, carbocyclyl, heterocyclyl, -$(CH_2)_n$$SiMe_3$, -$(CH_2)_n$$R^9$;

m and t are each independently an integer from 0 to 3;

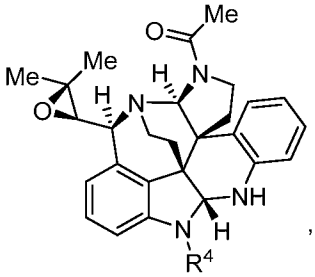
n, r, s, and v are each independently an integer from 0 to 4; and

u is 0, 1, or 2;

with the proviso that the compound of Formula (I) is not:

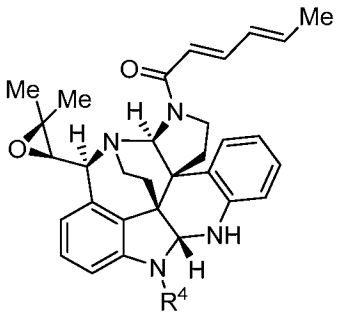


,



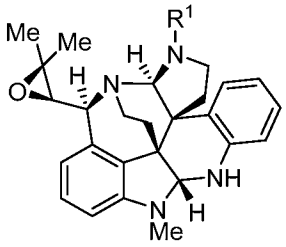
,

wherein R^4 is H or Me

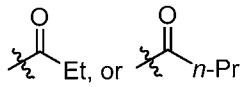


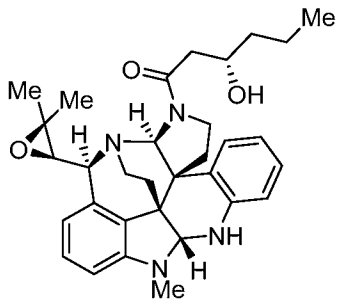
,

wherein R^4 is H, Me, or -CHO



, or

wherein R^1 is 



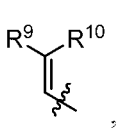
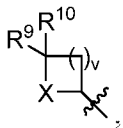
.

2. The compound of claim 1, wherein R^6 is H, C_1-C_{12} alkyl, C_1-C_{12} alkenyl, aryl, heteroaryl, carbocyclyl, or heterocyclyl.

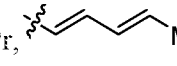
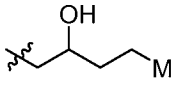
3. The compound of claim 1, wherein R^4 is H, -C(=O)R^9, C_1-C_{12} alkyl, aryl or heteroaryl.

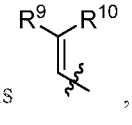
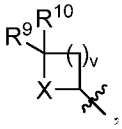
4. The compound of claim 1, wherein R^3 is H, C_1-C_{12} alkyl, or -S(=O)$_u$$R^{12}$.

5. The compound of claim 1, wherein R^2 and R^5 are each independently F, Br, Cl, I, C_1-C_{12} alkyl, aryl or heteroaryl.

6. The compound of claim 1, wherein R^6 is  , or  , and wherein X is O, NR^9, or $-S(=O)_uR^{12}$.

7. The compound of claim 6, wherein R^1 is $-C(=O)R^9$.

8. The compound of claim 7, wherein R^9 is Me, Et, *n*-Pr,  , or  .

9. The compound of claim 8, wherein R^6 is  , or  , and wherein X is O, NR^9, or $-S(=O)_uR^{12}$.

10. A pharmaceutical composition comprising a compound of Formula (I) and a pharmaceutically acceptable excipient.

11. A method of treating a disease or condition treatable with a compound of Formula (I), comprising administering an effective amount of a compound of claim 1 to a subject in need thereof.

12. The method of claim 11, wherein the disease or condition is cancer.

13. The method of claim 12, wherein the cancer is a cancer of the blood.

14. The method of claim 13, wherein the cancer of the blood is histiocytic leukemia, monocytic leukemia, Burkitt's lymphoma, Hodgkin's' lymphoma, T-cell leukemia, or B-cell leukemia.

15. The method of claim 11, wherein the disease or condition is a bacterial infection.

16. The method of claim 15, wherein the bacterial infection is an infection of *Escherichia coli*, *Klebsiella pneumoniae*, *Pseudomonas aeruginosa*, *Acinetobacter baumanii*, *Neisseria gonorrhoeae*, or *Bacillus subtilis*.

17. The method of claim 11, wherein the disease or condition is a fungal infection.

18. The method of claim 17, wherein the fungal infection is an infection of *Candida albicans*, *Trichophyton mentagrophytes*, or *Amorphotheca resinae*.

19. The method of claim 11, wherein the disease or condition is a viral infection.

20. The method of claim 19, wherein the viral infection is and infection of *Herpes simplex* type 1.

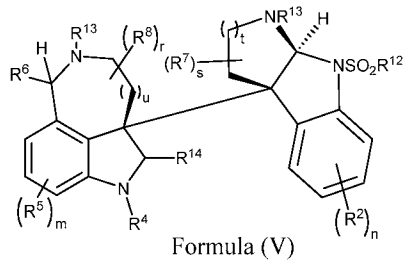
21. The method of claim 11, wherein the disease or condition is abnormal cardiovascular function.

22. The method of claim 21, wherein the abnormal cardiovascular function is bradycardia.

23. A method of treating an insect infestation, comprising contacting the insect with a compound of claim 1.

24. The method of claim 23, where in the insect infestation is caused by silkworms at the third instar larval stage.

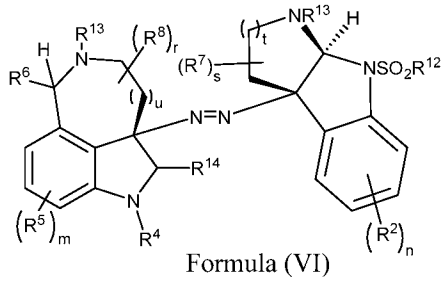
25. A method of making a compound of claim 1, comprising rearranging a compound of Formula (V):



Formula (V)

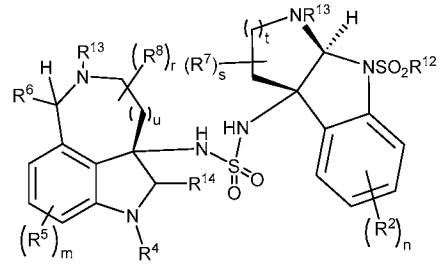
wherein R^{14} is -OH, -OR^9, -NR^9R^{10}, $S(O)_uR^{12}$, or $P(O)OR^9$.

26. The method of claim 25, wherein the compound of Formula (V) is prepared by a radical recombination reaction of a compound of Formula (VI):



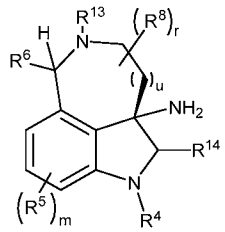
Formula (VI)

27. The method of claim 26, wherein the compound of Formula (VI) is prepared by the extrusion of sulfur dioxide from a compound of Formula (VII):

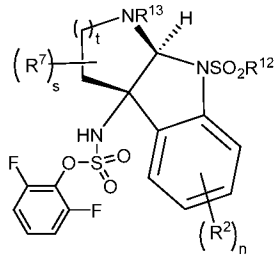


Formula (VII)

28. The method of claim 27, wherein the compound of Formula (VII) is prepared by reacting a compound of Formula (III) and a compound of Formula (VIII):

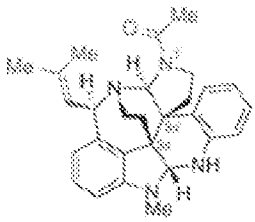


Formula (III)

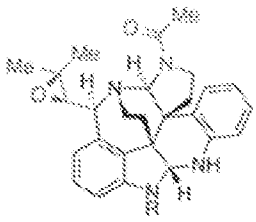


Formula (VIII)

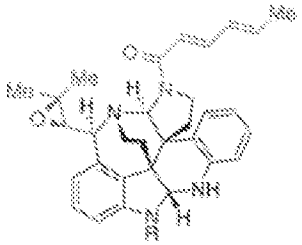
FIG 1.



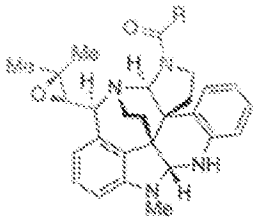
communesin F (1)



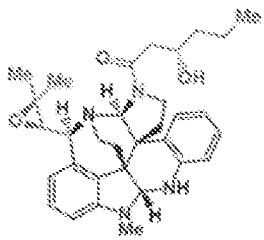
communesin A (2), R=Me
communesin E (3), R=H



communesin B (4), R=Me
communesin C (5), R=H
communesin D (6), R=CHO



communesin G (7), R=Et
communesin H (8), R=*n*-Pr



communesin I (9)

FIG 2.

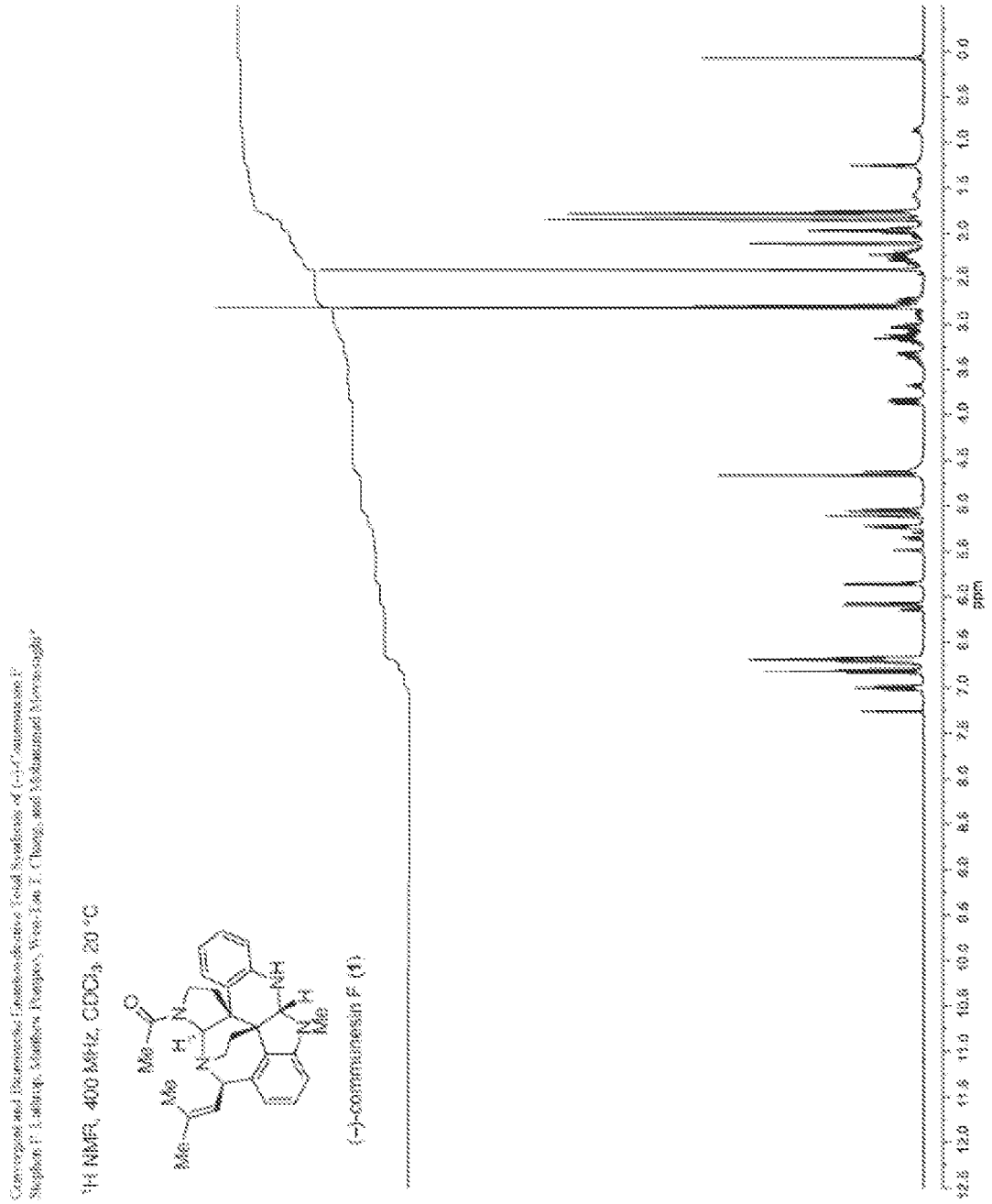

Concise and Enantioselective Total Synthesis of (+)-Communesin F
Stephen F. Martin, Matthew Pompeo, Wen-Jun T. Cheng, and Mohammad Movassaghi*
^{1}H NMR, 400 MHz, $CDCl_3$, 20 °C
(+)-communesin F (1)
ppm

FIG 3.

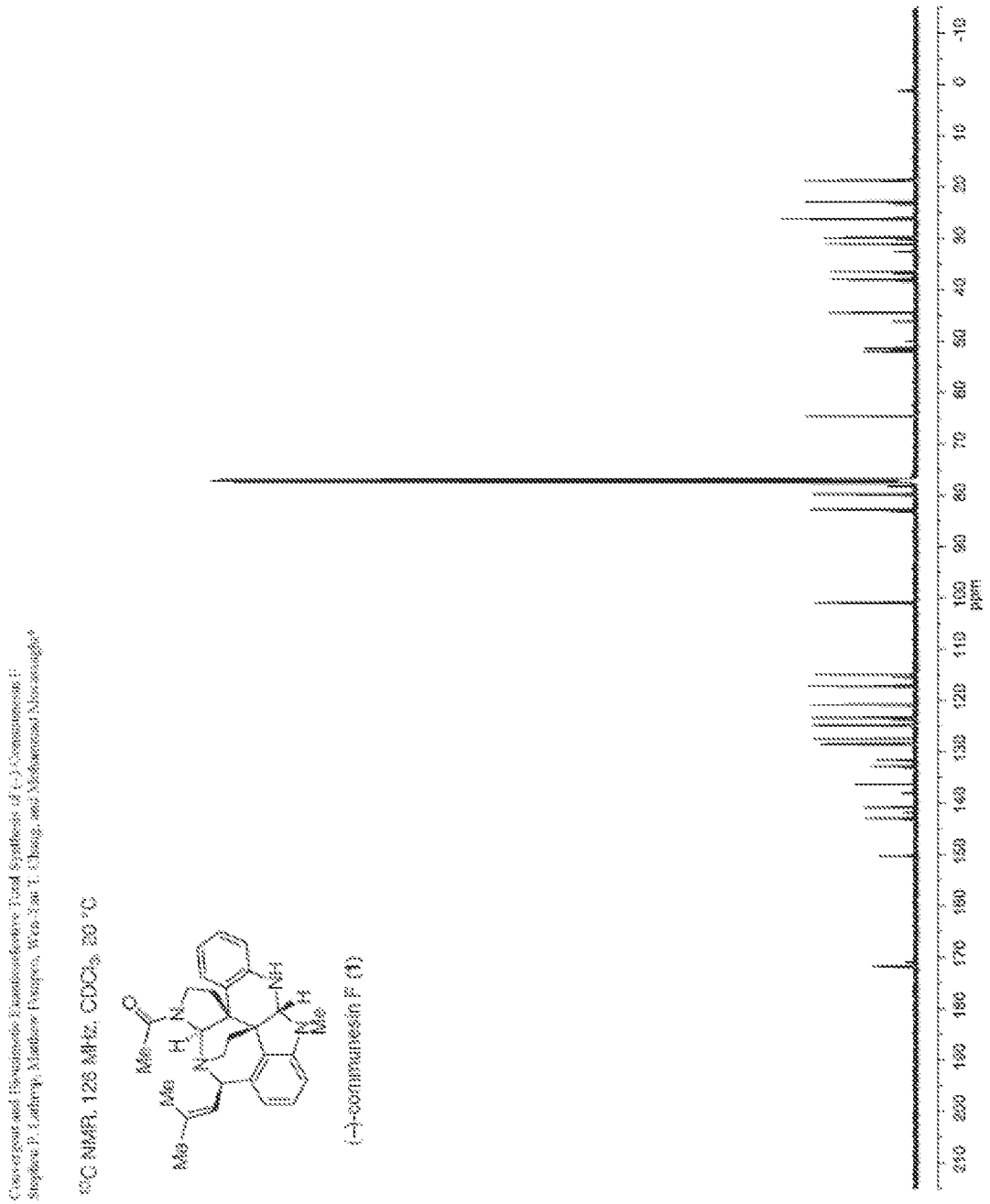
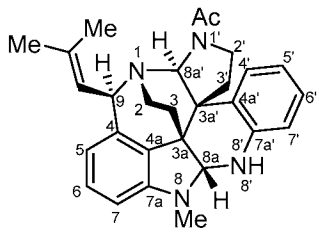

Convergent and Biomimetic Enantioselective Total Synthesis of (+)-Communesin F
Stephen P. Lathrop, Matthew Pompeo, Wen-Xue T. Chang, and Mohammad Movassaghi*
^{13}C NMR, 125 MHz, $CDCl_3$, 30 °C
(−)-communesin F (1)
ppm

FIG. 4



(–)-communesin F (**1**)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US17/32040

A. CLASSIFICATION OF SUBJECT MATTER
IPC - C07D 209/56, 221/02, 223/14 (2017.01)
CPC - C07D 209/56, 221/02, 223/14

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
See Search History document

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
See Search History document

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
See Search History document

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X --- Y	BELMAR, J. Total Syntheses of (+)-Isophellibiline and (+)-Communesin F, and Design, Synthesis and Pharmacological Evaluation of Dihydro-Beta-Erythroidine (DH beta E) Analogs. December 2012, pp. 1-179 [online], [retrieved on 2017-07-11]. Retrieved from the Internet <URL: https://etda.libraries.psu.edu/files/final_submissions/7513>; page 83, figure 5.1.1; page 84, paragraph 1; page 114, scheme 8.2.1; page 132, scheme 9.2.17	1-9, 23-24 --- 10-13, 15-16, 21
Y	US 2010/0125065 A1 (MOON, YC et al) 20 May 2010; abstract; paragraphs [0016], [0088], [0130]	10-13, 15-16, 21
Y	JADULCO, RC. Isolation and Structure Elucidation of Bioactive Secondary Metabolites from Marine Sponges and Sponge-derived Fungi. 2002, pp. 1-174 [online], [retrieved on 2017-07-11]. Retrieved from the Internet <URL: https://opus.bibliothek.uni-wuerzburg.de/files/296/dissertation9.pdf>; page 5, paragraph 2; page 72, paragraph 2; page 73, figure 2.49; page 85, paragraph 1; page 122, paragraph 2; page 145, paragraph 1	15-16
Y	CN 105198885 A (FIRST INST OF OCEANOGRAPHY) 30 December 2015, English translation; abstract	21
A	TROST, BM et al. Recent Advances on the Total Syntheses of the Communesin Alkaloids and Perophoramidine. Chemistry, Vol. 21, No. 46, 9 November 2015, pp. 16318–16343; page 29, scheme 1	25-28
A	YANG, J et al. Total Synthesis of (+)-Communesin F. Journal of American Chemical Society, Vol. 129, No. 45, 2007, pp. 13794-13795; page 13795, scheme 2a	25-28

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier application or patent but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
11 July 2017 (11.07.2017)	11 AUG 2017
Name and mailing address of the ISA/ Mail Stop PCT, Attn: ISA/US, Commissioner for Patents P.O. Box 1450, Alexandria, Virginia 22313-1450 Facsimile No. 571-273-8300	Authorized officer Shane Thomas PCT Helpdesk: 571-272-4300 PCT OSP: 571-272-7774

Form PCT/ISA/210 (second sheet) (January 2015)